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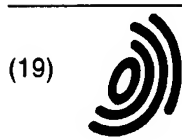
NOVEL AMINOBENZAMIDE DERIVATIVE

Abstract:

Abstract of EP1496052

This invention relates to a novel compound represented by the formula (I):
<CHEM> or a pharmaceutically acceptable salt thereof, wherein R<1> is -S(O)_p-A, -S(O)_q-B or -O-D, wherein p and q, which are the same or different, each represent an integer from 0 to 2, A is a straight chain C1-C10 alkyl group which may be substituted by R<10>, and B and D each independently represent R<12> which may be substituted by R<10>; R<2> is a hydrogen atom, a halogen atom, or a straight chain or branched C1-C6 alkyl group which may be substituted by R<10>; X<1> and X<2> each independently represent N or CH, but cannot both be N; the formula (II):
<CHEM> shows a monocyclic or bicyclic heteroaryl group which has a nitrogen atom adjacent to the carbon atom bonded to the amide group, and the heteroaryl group may be substituted by R<10>; R<10> is R<11>, or a hydrocarbon group which may be substituted by R<11>; R<11> is, for example, a hydrogen atom or amino; and R<12> is, for example, phenyl, thiazolyl, pyridyl or methylene dioxyphenyl. <??>The compound according to this invention has a glucokinase activation effect, and for example, is useful in the treatment and prevention of diabetes mellitus, and in the prevention of its complications such as diabetic nephropathy, diabetic retinopathy, diabetic neuropathy and diabetic arteriosclerosis. Data supplied from the esp@cenet database - Worldwide

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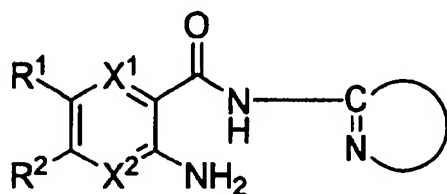
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(54) **NOVEL AMINOBENZAMIDE DERIVATIVE**

(57) This invention relates to a novel compound represented by the formula (I):



(I)

or a pharmaceutically acceptable salt thereof,

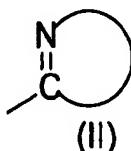
wherein

R^1 is $-S(O)_p-A$, $-S(O)_q-B$ or $-O-D$, wherein p and q , which are the same or different, each represent an integer from 0 to 2, A is a straight chain C1-C10 alkyl group which may be substituted by R^{10} , and B and D each independently represent R^{12} which may be substituted by R^{10} ;

R^2 is a hydrogen atom, a halogen atom, or a straight chain or branched C1-C6 alkyl group which may be substituted by R^{10} ;

X^1 and X^2 each independently represent N or CH, but cannot both be N;

the formula (II):



shows a monocyclic or bicyclic heteroaryl group which has a nitrogen atom adjacent to the carbon atom bonded to the amide group, and the heteroaryl group may be substituted by R^{10} ;

R^{10} is R^{11} , or a hydrocarbon group which may be substituted by R^{11} ;

R^{11} is, for example, a hydrogen atom or amino; and

R^{12} is, for example, phenyl, thiazolyl, pyridyl or methylene dioxyphenyl.

The compound according to this invention has a glucokinase activation effect, and for example, is useful in the treatment and prevention of diabetes mellitus, and in the prevention of its complications such as diabetic nephropathy, diabetic retinopathy, diabetic neuropathy and diabetic arteriosclerosis.

Description**Technical Field**

- 5 **[0001]** This invention relates to glucokinase activators containing aminobenzamide derivatives as active constituents, and to novel aminobenzamide derivatives or their salts.

Background Art

10 **[0002]** Glucokinase (GK) (ATP:D-hexose 6-phosphotransferase, EC 2.7.1.1) is one of the four types of mammalian hexokinases (hexokinase IV). Hexokinases are enzymes in the first step of the glycolysis pathway which catalyze the reaction from glucose to glucose-6-phosphate. Expression of glucokinase is largely localized in the liver and pancreatic beta cells, and it plays an important role in glucose metabolism throughout the body by controlling the rate limiting step of glucose metabolism in these cells. The glucokinase types expressed in the liver and pancreatic beta cells differ in
15 the sequence of the 15 N-terminal amino acids due to a difference in splicing, but their enzymatic properties are identical. The enzyme activities of the three hexokinases (I, II, III) other than glucokinase become saturated at a glucose concentration of below 1 mM, whereas the K_m of glucokinase for glucose is 8 mM, or close to the physiological glucose level. Thus, glucokinase-mediated intracellular glucose metabolism is accelerated in response to glucose level changes by postprandial glucose level increase (10-15 mM) from normal glucose (5 mM).

20 **[0003]** The theory that glucokinase acts as a glucose sensor for pancreatic beta cells and the liver has been advocated for about 10 years. Recent results in glucokinase gene-manipulated mice have confirmed that glucokinase does in fact play an important role in systemic glucose homeostasis. Mice lacking a functional glucokinase gene die shortly after birth, while mice overexpressing glucokinase have lower blood glucose levels. With glucose level increase, the reactions of pancreatic beta cells and the liver, while differing, both act toward lowering blood glucose. Pancreatic beta
25 cells secrete more insulin, while the liver takes up glucose and stores it as glycogen while also reducing glucose release.

[0004] Such variation in glucokinase enzyme activity is important for liver and pancreatic beta cell-mediated glucose homeostasis in mammals. A mutant form of the glucokinase gene is expressed in a type of diabetes which occurs in youth, known as MODY2 (maturity-onset diabetes of the young), and the reduced glucokinase activity has been shown to be responsible for blood glucose increase. On the other hand, families have been found having a mutation which
30 increases glucokinase activity, and such individuals exhibit hypoglycemic symptoms.

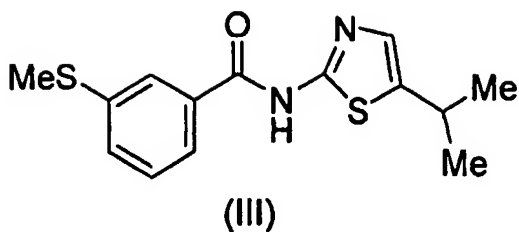
[0005] This suggests that in humans as well, glucokinase functions as a glucose sensor and thus plays an important role in glucose homeostasis. Glucose regulation utilizing a glucokinase sensor system should be possible to achieve in type II diabetic patients. Since glucokinase activators should have effects of accelerating insulin secretion by pancreatic beta cells and of promoting glucose uptake and inhibiting glucose release by the liver, they are potentially useful
35 as therapeutic agents for type II diabetic patients.

[0006] In recent years it has been demonstrated that pancreatic beta cell glucokinase is expressed locally in rat brain, and particularly in the ventromedial hypothalamus (VMH). Approximately 20% of VMH neurons are known as "glucose-responsive neurons", and these have long been considered to play an important role in body weight control. Administration of glucose into rat brain reduces feeding consumption, but inhibiting glucose metabolism by intracerebral
40 administration of the glucose analog glucosamine produces hyperphagia. Electrophysiological experiments have indicated that glucose-responsive neurons are activated in response to physiological glucose level changes (5-20 mM) but that their activation is inhibited with glucose metabolism inhibition by glucosamine or the like.

[0007] The glucose level-detecting system in the VMH is believed to be based on a glucokinase-mediated mechanism similar to that for insulin secretion by pancreatic beta cells. Consequently, substances which activate glucokinase in
45 the VMH in addition to the liver and pancreatic beta cells not only exhibit a blood glucose rectifying effect but can also potentially rectify obesity, which is a problem for most type II diabetic patients.

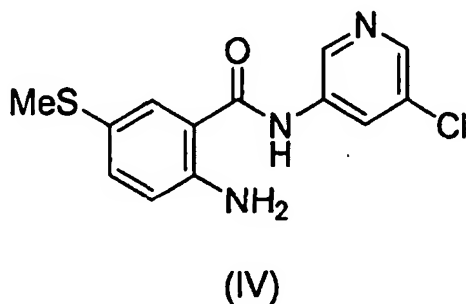
[0008] This indicates that compounds having glucokinase-activating effects are useful as therapeutic and/or prophylactic agents for diabetes, as therapeutic and/or prophylactic agents for diabetes complications such as retinopathy, nephropathy, neuropathy, ischemic heart disease, arteriosclerosis and the like, and as therapeutic and/or prophylactic
50 agents for obesity.

[0009] An example of a compound which is structurally similar to the present invention is the compound represented by the formula (III) disclosed by International Publication No. WO00/26202.



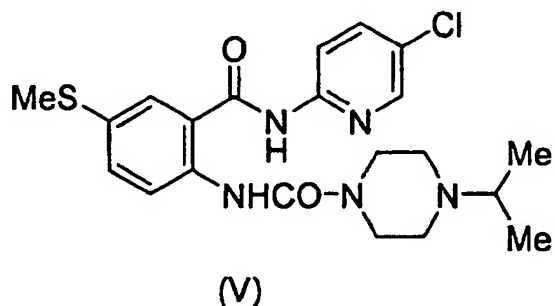
[0010] However, the aforesaid compound does not have an amino group in the benzamide skeleton, and is clearly different structurally from the compound of this application. Also, the compound in the aforesaid formula (III) is used as a CDK inhibitor and an anticancer agent, and in International Publication No. WO00/26202, there is no mention or suggestion regarding its use in diabetes mellitus.

[0011] The compound represented by the formula (IV) is disclosed by International Publication No. WO00/39118.



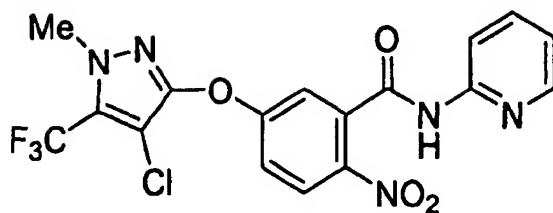
[0012] This compound (IV) does not have a nitrogen atom adjacent to the carbon atom bonded to the nitrogen atom of the NH group of carbamoyl, and differs structurally from the compound of this application. The aforesaid compound (V) is used in relation to Factor Xa, but it is different from the diabetes mellitus which is the usage described in this application. Also, in WO00/No. 39118 wherein the compound (IV) is disclosed, there is no mention or suggestion to the effect that it is useful as a treatment or prevention agent for diabetes mellitus.

[0013] The compound represented by the formula (V) is disclosed by International Publication No. WO00/39118.



[0014] However, this compound (V) has a piperazinyl group on the carbonyl side of the amide, and clearly differs structurally from the compound of this application. These compounds are related to Factor Xa inhibitor. Also, their usage is clearly different from diabetes mellitus which is the usage for the compound of this application, and there is no suggestion in this report that these compounds are useful in diabetes mellitus.

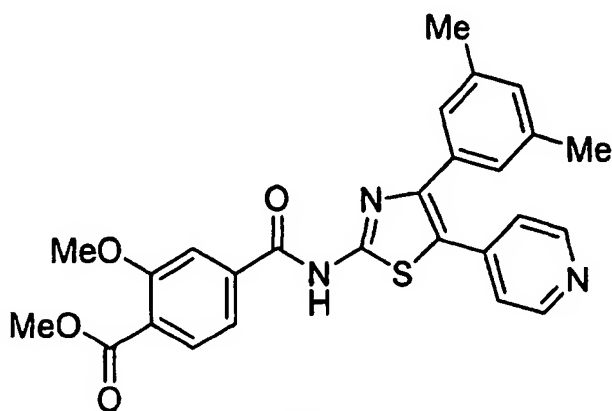
[0015] The compound represented by the formula (VI) is disclosed by Japanese Patent Application Laid-Open No. 64-25764.



(VI)

[0016] However, this compound has a nitro group in the benzamide skeleton, and differs structurally from the compound of this application which has an amino group.

[0017] The compound represented by the formula (VII) is disclosed by WO01/No. 10865 as an example of a compound which is effective in the treatment of diabetes mellitus.



(VII)

[0018] However, since the compound shown in formula (VII) has a methoxy group in R¹ and does not have an amino group in the benzamide skeleton, it differs structurally from the compound of this application.

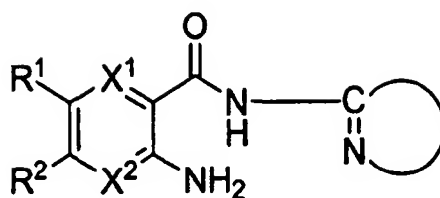
Disclosure of the Invention

[0019] It is an object of this invention to provide a diabetic treatment and/or preventive agent which combines with glucokinase and increases the activity of glucokinase, and to provide an anti-obesity agent which, by activating glucokinase, stimulates the satiety center.

[0020] The advantages of the compound according to this invention are that it has a superior effect to that of existing antidiabetic agents, and permits the development of new drug effects which were not present in existing antidiabetic agents.

[0021] The Inventors carried out extensive studies to develop a novel antidiabetic agent which, due to a different mechanism of action from that of existing drugs, had a superior pharmacological action to that of existing antidiabetic agents, and new pharmacological effects. As a result, they discovered that the compound represented by formula (I) has a glucokinase activation effect, and thus arrived at the present invention. Specifically, this invention relates to the following:

(1) A compound represented by the formula (I):



(I)

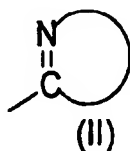
or a pharmaceutically acceptable salt thereof,

wherein

R¹ is -S(O)p-A, -S-(O)q-B or -O-D, wherein p and q, which are the same or different, each represent an integer from 0 to 2, A is a straight chain C1-C10 alkyl group which may be substituted by R¹⁰, and B and D each independently represent R¹² which may be substituted by R¹⁰;

R² is a hydrogen atom, a halogen atom, or a straight chain or branched C1-C6 alkyl group which may be substituted by R¹⁰;

X¹ and X² each independently represent N or CH, but cannot both be N;
the formula (II):



(II)

shows a monocyclic or bicyclic heteroaryl group which has a nitrogen atom adjacent to the carbon atom bonded to the amide group, and the heteroaryl group may be substituted by R¹⁰;

R¹⁰ is R¹¹, or a hydrocarbon group which may be substituted by R¹¹;

R¹¹ is a hydrogen atom, amino, carbamoyl, carbamoylamino, carbamoyloxy, carboxyl, cyano, sulfamoyl, trifluoromethyl, a halogen atom, hydroxyl, formyl, straight chain C1-C6 alkyl, C3-C9 cyclic hydrocarbon, aralkyl, N-aralkylamino, N,N-diaralkylamino, aralkyloxy, aralkylcarbonyl, N-aralkylcarbonyl, aryl, arylthio, N-arylamino, aryloxy, arylsulfonyl, arylsulfonyloxy, N-arylsulfonylamino, arylsulfamoyl, N-arylcarbonyl, aroyl, aroxy, C2-C6 alkanoyl, N-C2-C6 alkanoylamino, C1-C6 alkylthio, N-C1-C6 alkylsulfamoyl, N, N-di-C1-C6 alkylsulfamoyl, C1-C6 alkylsulfinyl, C1-C6 alkylsulfonyl, N-C1-C6 alkylsulfonylamino, C1-C6 alkoxy, C1-C6 alkoxycarbonyl or C1-C6 alkylamino; and

R¹² is phenyl, naphthyl, isoxazolyl, isothiazolyl, imidazolyl, oxazolyl, thiazolyl, thiadiazolyl, thienyl, triazolyl, tetrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrazolyl, pyrrolyl, pyranlyl, furyl, furazanyl, imidazolidinyl, tetrahydrofuranyl, piperazinyl, piperidinyl, pyrrolidinyl, morpholino, isoquinolyl, isoindolyl, indolyl, ethylene dioxyphenyl, methylene dioxyphenyl, quinolyl, pyridothiazolyl, dihydroindolyl, tetrahydroquinolyl, tetrahydroisoquinolyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, benzotriazolyl or benzofuranyl.

(2) The compound according to (1),

wherein

R¹⁰ in A is R¹¹¹, or a hydrocarbon group which may be substituted by R¹¹¹;

R¹² in B is a phenyl, isothiazolyl, imidazolyl, oxazolyl, thiazolyl, thiadiazolyl, thienyl, triazolyl, tetrazolyl, pyridyl, pyrimidinyl, furyl, ethylene dioxyphenyl, methylene dioxyphenyl, pyridothiazolyl, benzimidazolyl, benzothiazolyl or benzotriazolyl, and the foregoing functional groups may each be substituted by R¹⁰;

R¹⁰ in B is R¹¹¹, or a hydrocarbon group which may be substituted by R¹¹¹;

R¹² in D is a phenyl, naphthyl, pyridyl, pyrazinyl, pyrimidinyl, ethylene dioxyphenyl, methylene dioxyphenyl or quinolyl, and the foregoing functional groups may each be substituted by R¹⁰;

R¹⁰ in D is R¹¹¹, or a hydrocarbon group which may be substituted by R¹¹¹;

R¹⁰ in R² is R¹¹¹, or a hydrocarbon group which may be substituted by R¹¹¹;

R¹⁰ in the heteroaryl group represented by formula (II) is R¹¹², or a hydrocarbon group which may be substituted by R¹¹²;

the heteroaryl group of formula (II) is thiazolyl, imidazolyl, isothiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, triazolyl, oxazolyl, isoxazolyl, pyrazinyl, pyridyl, pyrimidinyl, pyridothiazolyl or benzothiazolyl;

R¹¹¹ is a hydrogen atom, carbamoyloxy, carboxyl, cyano, trifluoromethyl, a halogen atom, hydroxyl, straight chain C1-C6 alkyl, saturated C3-C9 cyclic hydrocarbon, aralkyl, aryl, arylthio, aroyl, aroxy, C1-C6 alkylthio, C1-C6 alkylsulfonyl, C1-C6 alkoxy or C1-C6 alkoxycarbonyl; and

R¹¹² is a hydrogen atom, carbamoyl, carboxyl, sulfamoyl, trifluoromethyl, a halogen atom, hydroxyl, aralkyl, aryl, arylthio, arylsulfonyl, aroyl, aroxy, C1-C6 alkylthio, C1-C6 alkylsulfinyl, C1-C6 alkylsulfonyl, C1-C6 alkoxy, C1-C6 alkoxycarbonyl or C3-C6 cycloalkyloxy.

(3) The compound according to (1),

wherein

R¹⁰ in A is R¹¹³, or a hydrocarbon group which may be substituted by R¹¹³;

R¹² in B is a phenyl, imidazolyl, oxazolyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidinyl, ethylene dioxyphenyl, methylene dioxyphenyl or pyridothiazolyl, and the foregoing functional groups may each be substituted by R¹⁰;

R¹⁰ in B is R¹¹³, or a hydrocarbon group which may be substituted by R¹¹³;

R¹² in D is a phenyl, naphthyl, pyridyl, ethylene dioxyphenyl or methylene dioxyphenyl, and the foregoing functional groups may each be substituted by R¹⁰;

R¹⁰ in D is R¹¹³, or a hydrocarbon group which may be substituted by R¹¹³;

R¹⁰ in R² is R¹¹³, or a hydrocarbon group which may be substituted by R¹¹³;

R¹¹³ is a hydrogen atom, carboxyl, trifluoromethyl, a halogen atom, hydroxyl, straight chain C1-C6 alkyl, saturated C3-C9 cyclic hydrocarbon, C1-C6 alkoxy, C1-C6 alkoxycarbonyl, C1-C6 alkylthio or C1-C6 alkylsulfonyl;

R¹⁰ in the heteroaryl group of formula (II) is R¹¹², or a hydrocarbon group which may be substituted by R¹¹²; and

the heteroaryl group of formula (II) is thiazolyl, imidazolyl, isothiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, triazolyl, oxazolyl, isoxazolyl, pyrazinyl, pyridyl, pyrimidinyl, pyridothiazolyl or benzothiazolyl.

(4) The compound according to (1),

wherein

R¹⁰ in A is R¹¹³, or a hydrocarbon group which may be substituted by R¹¹³;

R¹² in B is a phenyl, imidazolyl, oxazolyl, thiazolyl, thiadiazolyl, triazolyl, pyridyl, pyrimidinyl, ethylene dioxyphenyl, methylene dioxyphenyl or pyridothiazolyl, and the foregoing functional groups may each be substituted by R¹⁰;

R¹⁰ in B is R¹¹³, or a hydrocarbon group which may be substituted by R¹¹³;

R¹² in D is a phenyl, naphthyl, pyridyl, ethylene dioxyphenyl or methylene dioxyphenyl, and the foregoing functional groups may each be substituted by R¹⁰;

R¹⁰ in D is R¹¹³, or a hydrocarbon group which may be substituted by R¹¹³;

R¹⁰ in R² is R¹¹³, or a hydrocarbon group which may be substituted by R¹¹³;

R¹¹³ is a hydrogen atom, carboxyl, trifluoromethyl, a halogen atom, hydroxyl, straight chain C1-C6 alkyl, saturated C3-C9 cyclic hydrocarbon, C1-C6 alkoxy, C1-C6 alkoxycarbonyl, C1-C6 alkylthio or C1-C6 alkylsulfonyl;

R¹⁰ in formula (II) is R¹¹⁴, or a hydrocarbon group which may be substituted by R¹¹⁴; and

R¹¹⁴ is a hydrogen atom, carboxyl, trifluoromethyl, a halogen atom, hydroxyl, aryl, arylthio, straight chain C1-C6 alkyl, C1-C6 alkylthio, C1-C6 alkoxy or C1-C6 alkoxycarbonyl.

(5) The compound according to (4), wherein R¹ in formula (I) is -S(O)p-A or -S(O)q-B.

(6) The compound according to (4), wherein R¹ in formula (I) is -O-D.

(7) The compound according to (3), wherein both X¹ and X² in formula (I) are CH.

(8) The compound according to (3), wherein either X¹ or X² in formula (I) is a nitrogen atom.

(9) The compound according to (4), wherein both X¹ and X² in formula (I) are CH.

(10) The compound according to (4), wherein either X¹ or X² in formula (I) is a nitrogen atom.

(11) A glucokinase activator containing as an active constituent the compound according to any of (1) to (10).

(12) A treatment agent and/or preventive agent for diabetes mellitus containing as an active constituent the compound according to any of (1) to (10).

(13) A treatment agent and/or preventive agent for diabetes mellitus or obesity containing as an active constituent the compound according to any of (1) to (10).

(14) A treatment agent and/or preventive agent for obesity containing as an active constituent the compound according to any of (1) to (10).

[0022] The terms used in the present specification will now be described, while describing the invention in further detail.

[0023] An "aryl group" is, for example, a cyclic hydrocarbon aryl group having 6 to 14 carbon atoms such as phenyl,

naphthyl, biphenyl or anthryl group.

[0024] A "lower alkyl group" means a straight chain or branched alkyl group preferably having 1 to 6 carbon atoms. Examples are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isoamyl, neopentyl, isopentyl, 1,1-dimethylpropyl, 1-methylbutyl, 2-methylbutyl, 1,2-dimethylpropyl, hexyl, isohexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethylbutyl, 1,3-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1-ethylbutyl, 2-ethylbutyl, 1,2,2-trimethylpropyl and 1-ethyl-2-methylpropyl.

[0025] A "cycloalkyl group" means a saturated monocyclic hydrocarbon group having 3 to 9 carbon atoms. Examples are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

[0026] A "lower alkoxy group" means a group wherein the hydrogen atom of a hydroxyl group is substituted by the aforesaid lower alkyl group. Examples are methoxy, ethoxy, propoxy, isopropoxy, butoxy, sec-butoxy, tert-butoxy, pentyloxy, isopentyloxy, hexyloxy and isohexyloxy.

[0027] An "aralkyl group" means a lower alkyl group containing the aforesaid aryl group. Examples are benzyl, 1-phenylethyl, 2-phenylethyl, 1-naphthylmethyl and 2-naphthylmethyl.

[0028] An "aralkylamino group" means a group wherein a hydrogen atom of an amino group is monosubstituted by the aforesaid aralkyl group. Examples are benzylamino and phenethylamino.

[0029] A "diaralkylamino group" means a group wherein hydrogen atoms of identical or different amino groups are disubstituted by the aforesaid aralkyl groups. Examples are dibenzylamino and N-benzyl-2-phenylethylamino.

[0030] An "aralkylcarbamoyl group" means a group wherein a hydrogen atom bonded to the nitrogen atom of a carbamoyl group is monosubstituted by the aforesaid aralkyl group. For example, benzylcarbamoyl and phenylethylcarbamoyl are preferred.

[0031] An "alkylsulfamoyl group" means a group wherein a hydrogen atom of NH_2 of the aforesaid alkylsulfamoyl group is monosubstituted by the aforesaid alkyl group. For example, methylsulfamoyl, ethylsulfamoyl and isopropylsulfamoyl are preferred.

[0032] A "dialkylsulfamoyl group" means a group wherein the hydrogen atoms of NH_2 of the aforesaid alkylsulfamoyl group are disubstituted by the aforesaid alkyl groups which are identical or different. Examples are dimethylsulfamoyl, diethylsulfamoyl and methylethylsulfamoyl.

[0033] A "heteroaryl group" means a 4- to 7-membered single ring wherein this heteroaryl group has 1 to 3 hetero atoms selected from the group consisting of oxygen, sulfur and nitrogen atom, or a double ring wherein the heteroaryl group of this single ring is condensed with a benzene ring or pyridine ring. Examples are furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, thiadiazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyridyl, pyrimidinyl, pyrazinyl, quinolyl, isoquinolyl, quinazolinyl, quinolidinyl, quinoxalinyl, cinnolinyl, benzimidazolyl, imidazopyridyl, benzofuranyl, naphthylidiny, 1,2-benzisoxazolyl, benzoxazolyl, benzothiazolyl, oxazolopyridyl, pyridothiazolyl, isothiazolopyridyl and benzothieryl.

[0034] A "halogen atom" means, for example, a fluorine atom, a chlorine atom, a bromine atom or an iodine atom.

[0035] A "lower alkylcarbamoyl group" means a carbamoyl group monosubstituted by the aforesaid lower alkyl group. Examples are methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, isopropylcarbamoyl, butylcarbamoyl, sec-butylcarbamoyl and tert-butylcarbamoyl.

[0036] A "di-lower alkylcarbamoyl group" means a carbamoyl disubstituted by the aforesaid lower alkyl groups which are identical or different. Examples of "di-lower alkyl carbamoyl group" are dimethylcarbamoyl, diethylcarbamoyl, ethylmethylcarbamoyl, dipropylcarbamoyl, methylpropylcarbamoyl and diisopropyl carbamoyl.

[0037] A "lower alkylamino group" means an amino group monosubstituted by the aforesaid lower alkyl group. Examples are methylamino, ethylamino, propylamino, isopropylamino, butylamino, sec-butylamino or tert-butylamino.

[0038] A "di-lower alkylamino group" means an amino group disubstituted by the aforesaid lower alkyl groups which are identical or different. Examples are dimethylamino, diethylamino, dipropylamino, methylpropylamino or diisopropylamino.

[0039] An "aralkylamino group" means a group wherein a hydrogen atom of an amino group is monosubstituted by the aforesaid aralkyl group. Examples are benzylamino, phenylethylamino and 2-phenylethylamino.

[0040] A "diaralkylamino group" means a group wherein hydrogen atoms of amino groups are disubstituted by the aforesaid aralkyl groups. Examples are dibenzylamino, diphenylethylamino and benzylphenyl ethylamino. These aralkyl groups may be identical or different.

[0041] An "aralkyloxy group" means a group wherein the aforesaid aralkyl group is bonded to an oxygen atom. Examples are benzyloxy, phenylethyloxy and 2-phenylethyloxy.

[0042] An "aralkylcarbonyl group" means a group wherein the aforesaid aralkyl group is bonded to a carbonyl group. Examples are benzylcarbonyl and phenylethylcarbonyl.

[0043] An "aralkylcarbamoyl group" means a group wherein a hydrogen atom of a carbamoyl group is monosubstituted by the aforesaid aralkyl group. Examples are benzylcarbamoyl, phenylethylcarbamoyl and 2-phenylethylcarbamoyl.

[0044] An "arylthio group" means a group wherein the hydrogen atom of a thiol group is substituted by the aforesaid aryl group. Examples are phenylthio, naphthylthio and biphenylthio.

[0045] An "arylamino group" means a group wherein a hydrogen atom of an amino group is monosubstituted by the aforesaid aryl group. Examples are phenylamino, naphthylamino and biphenylamino.

[0046] An "aryloxy group" means a group wherein the hydrogen atom of a hydroxyl group is substituted by the aforesaid aryl group. Examples are phenyloxy, naphthyloxy and biphenyloxy.

[0047] An "arylsulfonyl group" means a group wherein the aforesaid aryl group is bonded to a sulfonyl group. Examples are phenylsulfonyl and naphthylsulfonyl.

[0048] An "arylsulfonyloxy group" means a group wherein the hydrogen atom of a hydroxyl group is substituted by the aforesaid arylsulfonyl group. Examples are phenylsulfonyloxy and biphenylsulfonyloxy.

[0049] An "arylsulfonylamino group" means a group wherein a hydrogen atom of an amino group is monosubstituted by the aforesaid arylsulfonyl group. Examples are phenylsulfonylamino, naphthylsulfonylamino and biphenylsulfonylamino.

[0050] An "arylsulfamoyl group" means a group wherein a hydrogen atom of a sulfamoyl group is monosubstituted by an aryl group. Examples are phenylsulfamoyl, naphthylsulfamoyl and biphenylsulfamoyl.

[0051] An "arylcarbamoyl group" means a group wherein a hydrogen atom of a carbamoyl group is monosubstituted by an aryl group. Examples are phenylcarbamoyl, naphthylcarbamoyl and biphenylcarbamoyl.

[0052] An "aroyl group" means a group wherein the aforesaid aryl group is bonded to a carbonyl group. Examples are phenylcarbonyl and naphthylcarbonyl.

[0053] An "aroxy group" means a group which wherein the aforesaid aroyl group is bonded to an oxygen atom. Examples are phenylcarbonyloxy and naphthylcarbonyloxy.

[0054] An "alkanoyl group" means a group wherein the aforesaid alkyl group is bonded to a carbonyl group. Examples are methylcarbonyl, ethylcarbonyl, propylcarbonyl and isopropylcarbonyl.

[0055] An "alkanoylamino group" means a group wherein the aforesaid alkanoyl group is bonded to an amino group. Examples are methylcarbonylamino, ethylcarbonylamino and isopropylcarbonylamino.

[0056] An "alkylthio group" means a group wherein the aforesaid alkyl group is bonded to a sulfur atom. Examples are methylthio, ethylthio, propylthio and isopropylthio.

[0057] An "alkylsulfamoyl group" means a group wherein a hydrogen atom of a sulfamoyl group is monosubstituted by the aforesaid alkyl group. Examples are methylsulfamoyl, ethylsulfamoyl, propylsulfamoyl and isopropylsulfamoyl.

[0058] A "dialkylsulfamoyl group" means a group wherein the hydrogen atoms of a sulfamoyl group are disubstituted by the aforesaid alkyl groups. Examples are dimethylsulfamoyl, diethylsulfamoyl and methyl ethylsulfamoyl. These alkyl groups may be identical or different.

[0059] An "alkylsulfinyl group" means a group wherein the aforesaid alkyl group is bonded to a sulfinyl group. Examples are methylsulfinyl, ethylsulfinyl and isopropylsulfinyl.

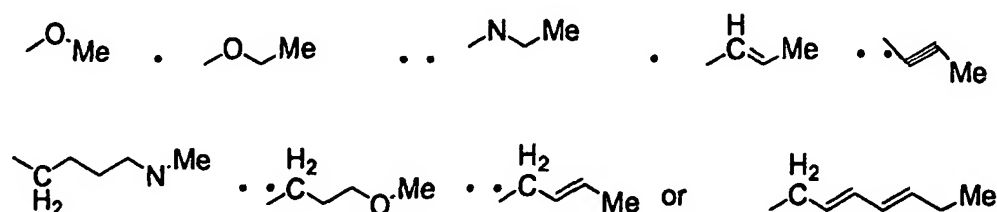
[0060] An "alkylsulfonyl group" means a group wherein the aforesaid alkyl group is bonded to a sulfonyl group. Examples are methylsulfonyl, ethylsulfonyl, propylsulfonyl and isopropylsulfonyl.

[0061] An "alkylsulfonylamino group" means a group wherein a hydrogen atom of an amino group is monosubstituted by the aforesaid alkylsulfonyl group. Examples are methylsulfonylamino, ethylsulfonylamino, propylsulfonylamino and isopropylsulfonylamino.

[0062] An "alkoxycarbonyl group" means a group wherein the hydrogen atom of a carboxyl group is substituted by the aforesaid alkyl group. Examples are methoxycarbonyl, ethoxycarbonyl, propylcarbonyl and isopropylcarbonyl.

[0063] A "hydrocarbon group" is a straight chain alkyl group having 1 to 6 carbon atoms, wherein 1 or 2, but preferably 1, of the carbon atoms forming this straight chain alkyl group may be substituted by a nitrogen atom, sulfur atom or oxygen atom, and/or carbon atoms in the straight chain alkyl group having 1 to 6 carbon atoms are connected by double bonds or triple bonds. The number of these double bonds or triple bonds is preferably 1 or 2, but more preferably 1.

[0064] Specifically, this hydrocarbon group is preferably methyl, ethyl, propyl, isopropyl, butyl, or the groups represented by the following formulae (VIII):



(VIII)

but more preferably methyl, ethyl, propyl, isopropyl, or the groups represented by the following formulae (IX) :



10 **[0065]** A "C3-C9 cyclic hydrocarbon group" means a group wherein the aforesaid hydrocarbon group which is a saturated or unsaturated hydrocarbon group having 3 to 9 carbon atoms forms a ring structure.

[0066] The C3-C9 cyclic hydrocarbon group is preferably a saturated cyclic hydrocarbon group having 3 to 9 carbon atoms.

15 **[0067]** More specifically, the C3-C9 cyclic hydrocarbon group is preferably cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, but more preferably cyclopropyl, cyclobutyl or cyclopentyl.

[0068] To more specifically describe the aminobenzamide derivative according to this invention, the various symbols used in the aforesaid formula (I) will be described referring to specific examples.

[0069] R¹ is -S(O)p-A, -S(O)q-B or -O-D.

[0070] p and q are each an integer from 0 to 2.

20 **[0071]** p and q are each preferably 0 or 2, but more preferably 0.

[0072] A is a straight chain C1-C10 alkyl group which may be substituted by R¹⁰.

[0073] The "straight chain C1-C10 alkyl group" of A is, for example, methyl, ethyl, propyl, butyl, pentyl or hexyl. Among these, methyl, ethyl, propyl or butyl is preferred, and methyl, ethyl or propyl is more preferred.

25 **[0074]** The straight chain C1-C10 alkyl group of A may be bonded to the hydrocarbon group of R¹⁰ to form a ring preferably containing 3 to 7 members. The ring structure of A is, for example, preferably cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

[0075] A is, for example, methyl, ethyl, propyl, cyclopropyl, isopropyl, butyl, pentyl, cyclopentyl, cyclohexyl or cycloheptyl. Among these, methyl, ethyl, propyl, isopropyl, butyl, cyclopentyl or cyclohexyl are more preferred, and methyl, ethyl, propyl, isopropyl, cyclopentyl or cyclohexyl are more preferred.

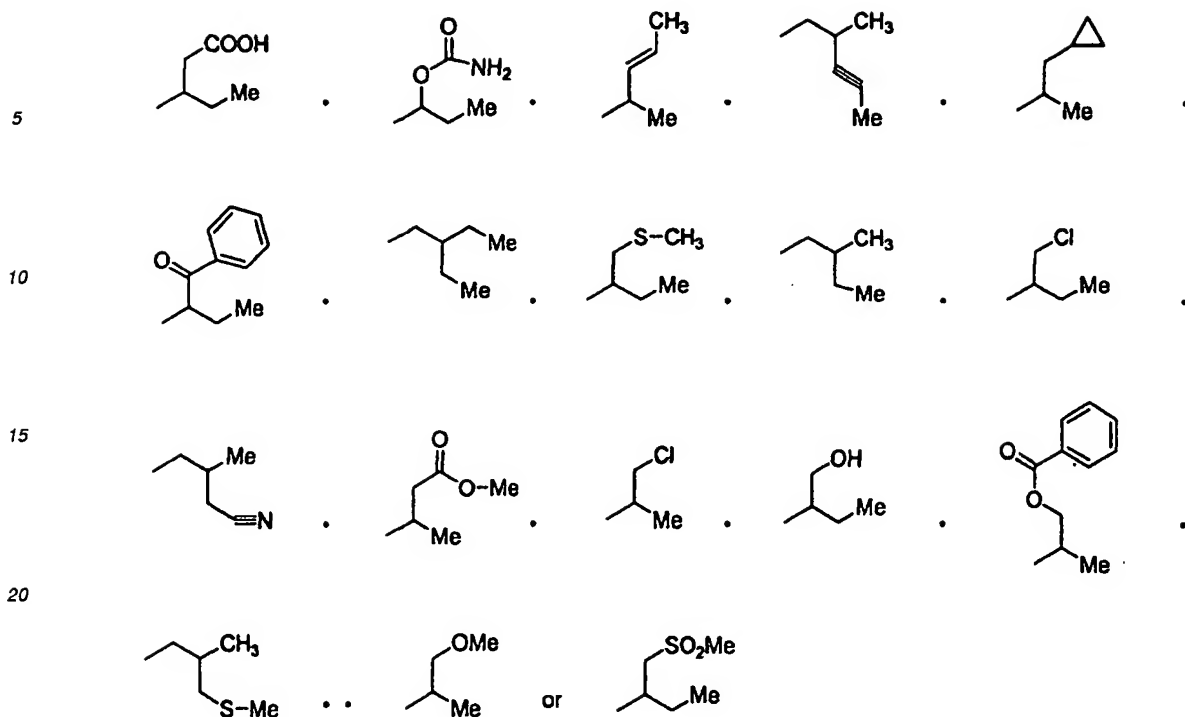
30 **[0076]** R¹⁰ is R¹¹, or a straight chain hydrocarbon group which may be substituted by R¹¹. R¹¹ is a hydrogen atom, amino, carbamoyl, carbamoylamino, carbamoyloxy, carboxyl, cyano, sulfamoyl, trifluoromethyl, a halogen atom, hydroxy, formyl, a C3-C9 cyclic hydrocarbon, aralkyl, N-aralkylamino, N,N-diaralkylamino, aralkyloxy, aralkylcarbonyl, N-aralkylcarbamoyl, aryl, arylthio, N-aryl amino, aryloxy, arylsulfonyl, arylsulfonyloxy, N-arylsulfonylamino, arylsulfamoyl, N-arylcarbamoyl, aroyl, aroxy, C2-C6 alkanoyl, N-C2-C6 alkanoylamino, C1-C6 alkylthio, N-C1-C6 alkylsulfamoyl, N, N-di-C1-C6 alkylsulfamoyl, C1-C6 alkylsulfinyl, C1-C6 alkylsulfonyl, N-C1-C6 alkylsulfonyl amino, C1-C6 alkoxy, C1-C6 alkoxycarbonyl or C1-C6 alkylamino.

[0077] R¹⁰ in A is preferably R¹¹¹, or a hydrocarbon group which may be substituted by R¹¹¹, but more preferably R¹¹³, or a hydrocarbon group which may be substituted by R¹¹³. Herein, R¹¹¹ is a hydrogen atom, straight chain C1-C6 alkyl, carbamoyloxy, carboxyl, cyano, trifluoromethyl, a halogen atom, hydroxy, a saturated C3-C9 cyclic hydrocarbon, aralkyl, aryl, aroyl, aroxy, C1-C6 alkylthio, C1-C6 alkoxy or C1-C6 alkoxycarbonyl. R¹¹³ is a hydrogen atom, straight chain C1-C6 alkyl, carboxyl, trifluoro methyl, a halogen atom, hydroxy, saturated C3-C9 cyclic hydrocarbon, C1-C6 alkoxy or C1-C6 alkoxycarbonyl.

40 **[0078]** Therefore, A is preferably methyl, ethyl, propyl, isopropyl, cyclopentyl, cyclohexyl, carbamoyloxymethyl, carbamoyloxyethyl, cyanomethyl, cyanoethyl, cyanopropyl, hydroxyethyl, carboxylmethyl, carboxylethyl, 1,2-dichloroethyl, 3-bromopropyl, 2-chloroethyl, cyclopropylmethyl, cyclopropylethyl, cyclopentylmethyl, cyclopropylethyl, phenethyl, benzyl, trifluoromethyl, phenacyl, ethylthiomethyl, naphthoylmethyl, methylthioethyl, propylthiomethyl, isopropylthioethyl, 2-methoxyethyl, 2-methoxy-1-methylethyl, isopropoxyethyl, methoxycarbonylmethyl, ethoxycarbonylmethyl, 2-methylsulfonylethyl, or the groups represented by the formulae (X):

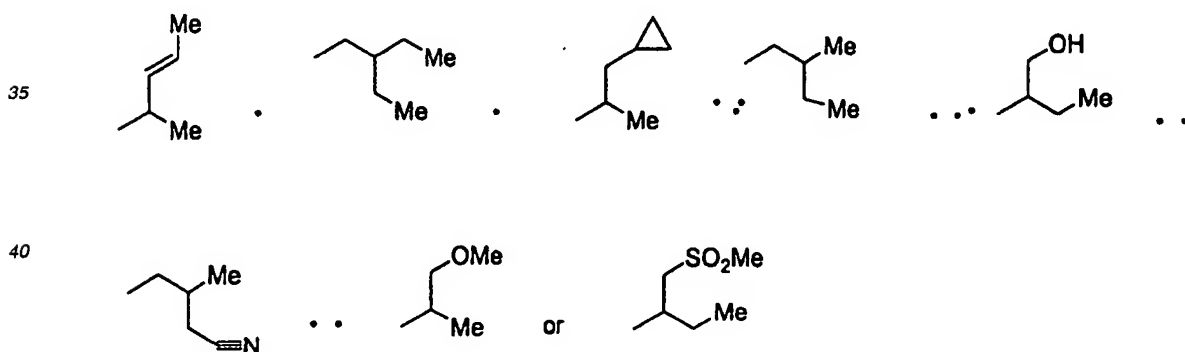
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• Formula • • • •

[0079] It is more preferably methyl, ethyl, isopropyl, cyclopentyl, cyclohexyl, cyanomethyl, 2-hydroxyethyl, cyclopropylmethyl, cyclopentylmethyl, trifluoromethyl, 2-methoxyethyl, or the groups represented by the formulae (XI):



Formula • • • • •

[0080] B is R¹² which may be substituted by R¹⁰.

[0081] R¹² in B is, for example, phenyl, naphthyl, isoxazolyl, isothiazolyl, imidazolyl, oxazolyl, thiazolyl, thiadiazolyl, thienyl, triazolyl, tetrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrazolyl, pyrrolyl, pyranal, furyl, furazanyl, imidazolidinyl, tetrahydrofuranyl, piperazinyl, piperidinyl, pyrrolidinyl, morpholino, isoquinolyl, isoindolyl, indolyl, ethylene dioxyphenyl, quinolyl, pyridothiazolyl, dihydroindolyl, tetrahydroquinolyl, tetrahydroisoquinolyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, benzotriazolyl, benzofuranyl or methylene dioxyphenyl.

[0082] R¹² in B is preferably phenyl, isothiazolyl, imidazolyl, oxazolyl, thiazolyl, thiadiazolyl, thienyl, triazolyl, tetrazolyl, pyridyl, pyrimidinyl, furyl, ethylene dioxyphenyl, methylene dioxyphenyl, benzimidazolyl, benzothiazolyl, benzotriazolyl or pyridothiazolyl, and the foregoing functional groups may each be substituted by R¹⁰. It is more preferably phenyl, imidazolyl, oxazolyl, thiazolyl, thiadiazolyl, triazolyl, pyridyl, pyrimidinyl, ethylene dioxyphenyl, methylene di-

oxyphenyl or pyridothiazolyl, and the foregoing functional groups may each be substituted by R¹⁰.

[0083] R¹⁰ in B is preferably R¹¹¹, or a hydrocarbon group which may be substituted by R¹¹¹, but more preferably R¹¹³, or a hydrocarbon group which may be substituted by R¹¹³. Herein, R¹¹¹ and R¹¹³ have identical definitions to R¹¹¹ and R¹¹³ in A respectively.

[0084] B is preferably phenyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-thiadiazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-imidazolyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 4-isothiazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 2-thienyl, 3-thienyl, 2-furyl, 3-furyl, triazol-3-yl, 5-tetrazolyl, 5-(1-methyl)tetrazolyl, 2,3-ethylene dioxyphenyl, 3,4-ethylene dioxyphenyl, 2,3-methylene dioxyphenyl, 3,4-methylene dioxyphenyl, benzimidazolyl, benzothiazolyl, 5-benzotriazolyl, 5-benzothiazolyl, 6-benzothiazolyl, 1,3-thiazolo-[5,4-b]pyridyl, 4-methyl-4H-[1,2,4] triazol-3-yl, 1-methyl-1H-imidazol-2-yl, 4,5-dimethyl-4H-[1,2,4]triazol-3-yl, 4-methyl-5-trifluoromethyl-4H-[1,2,4]triazol-3-yl, 5-methyl-1,2,4-triazol-3-yl, 5-tetrazolyl, 4-carbamoyloxymethylphenyl, 3-carbamoyloxymethylphenyl, 4-methoxycarbonylmethylphenyl, 4-cyanophenyl, 4-hydroxyphenyl, 3-carboxyphenyl, 4-trifluoromethylphenyl, 2-methylthiophenyl, 3-methylthiophenyl, 4-methylthiophenyl, 4-methoxyphenyl, 3-ethoxycarbonylphenyl, 2-methoxycarbonylphenyl, 4-methylsulfonylphenyl, 2-(4-carbamoyl)thiazolyl, 2-(4-carbamoyloxy)thiazolyl, 2-(5-cyano)thiazolyl, 2-(5-hydroxymethyl)thiazolyl, 2-(4-carboxy)thiazolyl, 2-(4-carboxy)thiazolyl, 2-(5-bromo)thiazolyl, 2-(4-ethylthio)thiazolyl, 2-(5-trifluoromethyl)thiazolyl, 2-(4-methoxymethyl)thiazolyl, 2-(4-methoxycarbonyl)thiazolyl, 2-(4-methylsulfonyl)thiazolyl, 2-(5-carbamoyl)thiadiazolyl, 2-(5-carbamoyloxy)thiadiazolyl, 2-(5-cyano)thiadiazolyl, 2-(5-hydroxy)thiadiazolyl, 2-(5-carboxy)thiadiazolyl, 2-(5-bromo)thiadiazolyl, 2-(5-methylthio)thiadiazolyl, 2-(5-trifluoromethyl)thiadiazolyl, 2-(5-methoxymethyl)thiadiazolyl, 2-(5-methoxycarbonyl)thiadiazolyl, 2-(5-methylsulfonyl)thiadiazolyl, 5-(3-carboxy)thiadiazolyl, 5-(3-hydroxymethyl)thiadiazolyl, 5-(3-carbamoyl)thiadiazolyl, 5-(3-trifluoromethyl)thiadiazolyl, 5-(3-methylthio)thiadiazolyl, 5-(3-methoxymethyl)thiadiazolyl, 5-(3-methoxycarbonyl)thiadiazolyl, 5-(3-methylsulfonyl)thiadiazolyl, 2-(5-carbamoyloxy)triazolyl, 2-(5-cyano)triazolyl, 2-(5-hydroxymethyl)triazolyl, 2-(5-carboxy)triazolyl, 2-(5-trifluoromethyl)triazolyl, 2-(5-methylthio)triazolyl, 2-(5-methoxymethyl)triazolyl, 2-(5-methoxycarbonyl)triazolyl, 2-(5-methylsulfonyl)triazolyl, 2-(3-carbamoyl)pyridyl, 2-(3-carbamoyloxy)pyridyl, 2-(4-cyano)pyridyl, 2-(5-hydroxy)pyridyl, 2-(4-carboxy)pyridyl, 2-(5-trifluoromethyl)pyridyl, 2-(4-methylthio)pyridyl, 2-(5-methoxy)pyridyl, 2-(5-methoxycarbonyl)pyridyl, 2-(4-methylsulfonyl)pyridyl, 2-(6-carbamoyl)pyrimidinyl, 2-(5-carbamoyloxy)pyrimidinyl, 2-(5-cyano)pyrimidinyl, 2-(5-hydroxy)pyrimidinyl, 2-(5-carboxy)pyrimidinyl, 2-(5-trifluoromethyl)pyrimidinyl, 2-(5-ethylthiomethyl)pyrimidinyl, 2-(5-methoxy)pyrimidinyl, 2-(5-ethoxycarbonyl)pyrimidinyl, 2-(5-methylsulfonyl)pyrimidinyl, 2-(4-carboxymethyl)thiazolyl, 2-(5-carbamoyloxymethyl)thiazolyl, 2-(5-chloromethyl)thiazolyl, 2-(5-methoxycarbonylmethyl)thiazolyl, 3-(5-carboxymethyl)-1,2,4-triazol-3-yl, 5-carbamoyloxymethyl-1,2,4-triazol-3-yl, 5-methoxycarbonylmethyl-1,2,4-triazol-2-yl, 5-cyanomethyl-1,2,4-triazol-2-yl, 5-methylsulfonylmethyl-1,2,4-triazol-2-yl, 5-methylsulfanylmethyl-1,2,4-triazol-2-yl, 2-(5-carboxymethyl)thiadiazolyl, 2-(5-carbamoyloxymethyl)thiadiazolyl, 2-(5-cyanomethyl)thiadiazolyl, 2-(5-methoxycarbonylmethyl)thiadiazolyl, 2-(5-methylsulfonylmethyl)thiadiazolyl or 2-(5-methylsulfanylmethyl)thiadiazolyl. However, it is more preferably phenyl, 2-thiazolyl, 2-thiadiazolyl, 2-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-triazolyl, 5-tetrazolyl, 2,3-methylene dioxyphenyl, 4-methylene dioxyphenyl, 1,3-thiazolo[5,4-b]pyridyl, 4-methyl-4H-[1,2,4]triazol-3-yl, 1-methyl-1H-imidazol-2-yl, 4,5-dimethyl-4H-[1,2,4]triazol-3-yl, 4-methyl-5-trifluoromethyl-4H-[1,2,4]triazol-3-yl, 5-methyl-1,2,4-triazol-3-yl, 4-cyanophenyl, 4-trifluoromethylphenyl, 2-methylthiophenyl, 3-methylthiophenyl, 4-methylthiophenyl, 4-methoxyphenyl, 2-methoxycarbonylphenyl, 4-methoxycarbonylmethylphenyl, 4-methylsulfonylphenyl, 2-(5-hydroxymethyl)thiazolyl, 2-(5-trifluoromethyl)thiazolyl, 2-(4-methoxymethyl)thiazolyl, 2-(5-cyano)thiadiazolyl, 2-(5-chloromethyl)thiazolyl, 2-(5-methoxycarbonyl)thiazolyl, 2-(5-hydroxy)thiadiazolyl, 2-(5-trifluoromethyl)thiadiazolyl, 2-(5-methoxymethyl)thiadiazolyl, 2-(5-methoxycarbonylmethyl)thiadiazolyl, 5-(3-hydroxymethyl)thiadiazolyl, 5-(3-trifluoromethyl)thiadiazolyl, 5-(3-methoxymethyl)thiadiazolyl, 5-(3-methoxycarbonyl)thiadiazolyl, 2-(5-cyanomethyl)thiadiazolyl, 2-(5-methylsulfonylmethyl)thiadiazolyl, 2-(5-methylsulfanylmethyl)thiadiazolyl, 2-(5-cyano)triazolyl, 2-(5-hydroxymethyl)triazolyl, 2-(5-trifluoromethyl)triazolyl, 2-(5-methoxymethyl)triazolyl, 2-(5-methoxycarbonyl)triazolyl, 2-(5-methoxycarbonylmethyl)triazolyl, 2-(5-cyanomethyl)triazolyl, 2-(5-methylsulfonylmethyl)triazolyl, 2-(5-methylsulfanylmethyl)triazolyl, 2-(4-cyano)pyridyl, 2-(5-hydroxy)pyridyl, 2-(5-trifluoromethyl)pyridyl, 2-(5-methoxy)pyridyl, 2-(5-methoxycarbonyl)pyridyl, 2-(5-cyano)pyrimidinyl, 2-(5-hydroxy)pyrimidinyl, 2-(5-trifluoromethyl)pyrimidinyl or 2-(5-methoxy)pyrimidinyl.

[0085] D is R¹² which may be substituted by R¹⁰. R¹⁰ and R¹² are as previously defined.

[0086] R¹² in D is preferably phenyl, naphthyl, pyridyl, ethylene dioxyphenyl or methylene dioxyphenyl. It is more preferably phenyl, pyridyl, methylene dioxyphenyl or ethylene dioxyphenyl, and the foregoing functional groups may each be substituted by R¹⁰.

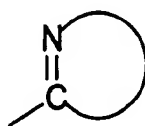
[0087] R¹⁰ in D is preferably R¹¹¹, or a hydrocarbon group which may be substituted by R¹¹¹, but more preferably R¹¹³, or a hydrocarbon group which may be substituted by R¹¹³. Herein, R¹¹¹ and R¹¹³ are as previously defined.

[0088] R² is a hydrogen atom, a halogen atom, or a C1-C6 alkyl group which may be substituted by R¹⁰. R¹⁰ in R² is preferably R¹¹¹, or a hydrocarbon group which may be substituted by R¹¹¹, but more preferably R¹¹³, or a hydrocarbon group which may be substituted by R¹¹³. R¹¹¹ and R¹¹³ are as previously defined.

[0089] Therefore, more specifically, D is preferably phenyl, 1-naphthyl, 2-naphthyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 3,4-ethylene dioxyphenyl, 2,3-ethylene dioxyphenyl, 2,3-methylene dioxyphenyl, 3,4-methylene dioxyphenyl, 4-tolyl,

3-carbamoylphenyl, 4-carbamoyloxyphenyl, 4-carboxyphenyl, 2-cyanophenyl, 4-trifluoromethylphenyl, 4-chlorophenyl, 2-fluorophenyl, 2,4-difluorophenyl, 3-bromophenyl, 4-hydroxyphenyl, 4-methylthiophenyl, 2-fluoro-4-methylsulfonylphenyl, 2-methoxy-4-fluorophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxycarbonylphenyl, 2-methylsulfonylphenyl, 4-fluoro-2-methylsulfonylphenyl, 3-methylsulfonylphenyl, 4-methylsulfonylphenyl, 2-(4-carbamoyl)pyridyl, 3-(5-trifluoromethyl)pyridyl, 3-(6-methoxycarbonyl)pyridyl, 3-carboxyphenyl, 3-carbamoyloxymethylphenyl, 3-hydroxymethylphenyl, 4-cyanomethylphenyl, 4-methylthiomethylphenyl, 3-methylsulfonylmethylphenyl, 3-methoxycarbonylmethylphenyl, 2-(5-carboxy)pyridyl, 3-(5-cyanomethyl)pyridyl, 2-(5-methylthio)pyridyl, 2-(4-methoxymethyl)pyridyl or 3-(5-methylsulfonyl)pyridyl, but more preferably phenyl, 2-pyridyl, 4-pyridyl, 2,3-methylene dioxyphenyl, 3,4-methylene dioxyphenyl, 4-tolyl, 2-cyanophenyl, 4-trifluoromethylphenyl, 4-chlorophenyl, 2-fluorophenyl, 2,4-difluorophenyl, 4-methylthiophenyl, 2-fluoro-4-methylsulfonylphenyl, 2-methoxy-4-fluorophenyl, 2-methoxyphenyl, 3-methoxyphenyl, 2-methylsulfonylphenyl, 4-fluoro-2-methylsulfonylphenyl, 3-methylsulfonylphenyl, 4-methylsulfonylphenyl, 3-(5-trifluoromethyl)pyridyl, 3-(6-methoxycarbonyl)pyridyl, 3-hydroxymethylphenyl, 4-methylthiomethylphenyl, 3-methylsulfonylphenyl, 2-(4-methoxymethyl)pyridyl or 3-(5-methylsulfonyl)pyridyl.

[0090] The formula (II) is a monocyclic or bicyclic heteroaryl group which may be substituted by R¹⁰ containing a nitrogen atom next to the carbon atom combined with the amide group.



(II)

[0091] The monocyclic or bicyclic heteroaryl group of the aforesaid formula (II) is preferably, for example, 2-thiazolyl, 4-thiazolyl, 2-imidazolyl, 3-isothiazolyl, 1,2,4-thiadiazol-3-yl, 1,2,4-thiadiazol-5-yl, 1,3,4-thiadiazol-2-yl, 2-triazolyl, 2-oxazolyl, 3-isoxazolyl, pyrazinyl, 2-pyridyl, 2-pyrimidinyl, 3-pyrido-[3,2-d][1,3]thiazol-2-yl or 2-benzothiazolyl.

[0092] R¹⁰ in the aforesaid formula (II) is preferably R¹¹², or a hydrocarbon group which may be substituted by R¹¹², but more preferably R¹¹⁴, or a hydrocarbon group which may be substituted by R¹¹⁴. Here, R¹¹² is, for example, a hydrogen atom, carbamoyl, carboxyl, sulfamoyl, trifluoromethyl, a halogen atom, hydroxy, aralkyl, aryl, arylthio, arylsulfonyl, aroyl, aroxy, straight chain C1-C6 alkyl, C1-C6 alkylthio, C1-C6 alkylsulfinyl, C1-C6 alkylsulfonyl, C1-C6 alkoxy, C1-C6 alkoxy carbonyl or C3-C6 cycloalkyloxy. R¹¹⁴ is, for example, a hydrogen atom, carboxyl, trifluoromethyl, a halogen atom, hydroxy, aryl, arylthio, straight chain C1-C6 alkyl, C1-C6 alkylthio, C1-C6 alkoxy or C1-C6 alkoxy carbonyl.

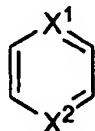
[0093] Therefore, more specifically, a group represented by formula (II) is preferably, for example, 2-thiazolyl, 2-imidazolyl, 3-isothiazolyl, 1,3,4-thiadiazol-2-yl, 1,2,4-thiadiazol-5-yl, 2-oxazolyl, isoxazol-3-yl, 2-pyridyl, 2-pyrazinyl, 2-pyrimidinyl, 2-benzothiazolyl, 2-(4-carbamoyl)thiazolyl, 2-(4-carbamoyloxy)thiazolyl, 2-(5-cyano)thiazolyl, 2-(4-hydroxymethyl)thiazolyl, 2-(5-hydroxymethyl)thiazolyl, 2-(4-carboxy)thiazolyl, 2-(5-bromo)thiazolyl, 2-(5-chloro)thiazolyl, 2-(5-chloro-4-methyl)thiazolyl, 4-(1-methoxyethyl)thiazol-2-yl, 2-(4-methoxymethyl)thiazolyl, 2-(4-trifluoromethyl)thiazolyl, 2-(4-isopropyl)thiazolyl, 2-(4-methyl)thiazolyl, 4-(1-hydroxyethyl)thiazol-2-yl, 2-(4-ethylthio)thiazolyl, 2-(5-trifluoromethyl)thiazolyl, 2-(4-methoxymethyl)thiazolyl, 2-(4-methoxycarbonyl)thiazolyl, 2-(4-methylsulfonyl)thiazolyl, 4-(4-methyl-4H-[1,2,4]triazol-2-ylsulfanylmethyl)thiazol-2-yl, 4-(5-methyl-4H-[1,2,4]triazol-2-ylsulfanylmethyl)thiazol-2-yl, 2-(5-carbamoyl)thiadiazolyl, 2-(5-carbamoyloxy)thiadiazolyl, 2-(5-cyano)thiadiazolyl, 2-(5-hydroxymethyl)thiadiazolyl, 2-(5-carboxy)thiadiazolyl, 2-(5-bromo)thiadiazolyl, 2-(5-methylthio)thiadiazolyl, 2-(5-trifluoromethyl)thiadiazolyl, 2-(5-methoxymethyl)thiadiazolyl, 2-(5-methoxycarbonyl)thiadiazolyl, 2-(5-methylsulfonyl)thiadiazolyl, 5-(3-carboxy)thiadiazolyl, 5-(3-hydroxymethyl)thiadiazolyl, 5-(3-carbamoyl)thiadiazolyl, 5-(3-trifluoromethyl)thiadiazolyl, 5-(3-methylthio)thiadiazolyl, 5-(3-methoxymethyl)thiadiazolyl, 5-(3-methoxycarbonyl)thiadiazolyl, 5-(3-methylsulfonyl)thiadiazolyl, 2-(4-carbamoyl)pyridyl, 2-(4-carbamoyloxy)pyridyl, 2-(5-cyano)pyridyl, 2-(5-hydroxymethyl)pyridyl, 2-(4-carboxy)pyridyl, 2-(5-bromo)pyridyl, 2-(4-ethylthio)pyridyl, 2-(5-trifluoromethyl)pyridyl, 2-(4-methoxy)pyridyl, 2-(4-methoxymethyl)pyridyl, 2-(4-methoxycarbonyl)pyridyl, 2-(4-methylsulfonyl)pyridyl, 3-pyrido-[3,2-d][1,3]thiazol-2-yl, 2-(5-carbamoyl)thiadiazolyl, 2-(5-carbamoyloxy)thiadiazolyl, 2-(5-cyano)thiadiazolyl, 4-(6-carbamoyl)pyrimidinyl, 4-(5-carbamoyloxy)pyrimidinyl, 4-(6-cyano)pyrimidinyl, 4-(6-hydroxymethyl)pyrimidinyl, 4-(5-carboxy)pyrimidinyl, 4-(5-trifluoromethyl)pyrimidinyl, 4-(5-ethylthiomethyl)pyrimidinyl, 4-(5-methoxymethyl)pyrimidinyl, 4-(5-ethoxycarbonyl)pyrimidinyl, 4-(5-methylsulfonyl)pyrimidinyl, 2-(5-chloromethyl)thiazolyl, 2-(5-methoxycarbonylmethyl)thiazolyl, 2-(4-carboxylmethylmethyl)thiazolyl, 2-(5-carbamoyloxymethyl)thiazolyl, 3-(5-methoxymethyl)thiazolyl, 3-(5-methoxycarbonylmethyl)thiazolyl, 5-methylsulfonylmethyl-1,3,4-thiadiazol-2-yl, 5-methylthiomethyl-1,3,4-thiadiazol-2-yl, 5-carboxyme-

thyl-1,3,4-thiadiazol-2-yl, 5-carbamoyloxymethyl-1,3,4-thiadiazol-2-yl, 5-cyanomethyl-1,3,4-thiadiazol-2-yl, 5-methoxycarbonylmethyl-1,3,4-thiadiazol-2-yl, 5-hydroxymethyl-1,3,4-thiadiazol-2-yl or 5-methoxymethyl-1,3,4-thiadiazol-2-yl, but more preferably 2-thiazolyl, 3-isothiazolyl, 1,3,4-thiadiazol-2-yl, 1,2,4-thiadiazol-5-yl, 2-pyridyl, 2-(4-carbamoyloxy)thiazolyl, 2-(5-cyano)thiazolyl, 2-(5-hydroxymethyl)thiazolyl, 2-(4-carboxy)thiazolyl, 2-(5-bromo)thiazolyl, 2-(5-trifluoromethyl)thiazolyl, 2-(4-methoxymethyl)thiazolyl, 2-(4-methoxycarbonyl)thiazolyl, 2-(4-methylsulfonyl)thiazolyl, 2-(5-cyano)thiadiazolyl, 2-(5-methylthio)thiadiazolyl, 2-(5-methoxycarbonyl)thiadiazolyl, 2-(5-methylsulfonyl)thiadiazolyl, 5-(3-hydroxymethyl)thiadiazolyl, 5-(3-methoxymethyl)thiadiazolyl, 5-(3-methoxycarbonyl)thiadiazolyl, 2-(4-carbamoyloxy)pyridyl, 2-(5-cyano)pyridyl, 2-(5-hydroxymethyl)pyridyl, 2-(5-bromo)pyridyl, 2-(5-trifluoromethyl)pyridyl, 2-(4-methoxy)pyridyl, 2-(4-methoxymethyl)pyridyl, 2-(4-methoxycarbonyl)pyridyl, 3-pyrido-[3,2-d] [1,3]thiazol-2-yl, 4-(6-cyano)pyrimidinyl, 4-(6-hydroxymethyl)pyrimidinyl, 4-(5-trifluoromethyl)pyrimidinyl, 4-(5-methoxymethyl)pyrimidinyl, 2-(5-chloromethyl)thiazolyl, 2-(5-methoxycarbonylmethyl)thiazolyl, 5-methylsulfonylmethyl-1,3,4-thiadiazol-2-yl, 5-methylthiomethyl-1,3,4-thiadiazol-2-yl or 5-methoxycarbonylmethyl-1,3,4-thiadiazol-2-yl.

[0094] R² is a hydrogen atom, a halogen atom, or a C1-C6 alkyl group which may be substituted by R¹⁰. R¹⁰ in R² is preferably R¹¹¹, or a hydrocarbon group which may be substituted by R¹¹¹, but more preferably R¹¹³, or a hydrocarbon group which may be substituted by R¹¹³. R¹¹¹ and R¹¹³ are as previously defined.

[0095] R² is more preferably methyl, ethyl, propyl, isopropyl, a fluorine atom or a hydrogen atom.

[0096] Preferably, X¹ and X² of a group represented by the following formula (XII) in formula (I) are both CH, or X¹ is a nitrogen atom and X² is CH, but more preferably, X¹ and X² are both CH.



(XII)

[the symbols in the formula are as previously defined]

[0097] R¹ is -S(O)p-A, -S(O)q-B or -O-D. Among these, -S(O)p-B or -O-D is preferred.

[0098] R² is a hydrogen atom, a halogen atom, or a C1-C10 alkyl group which may be substituted by R¹⁰. Among these, a hydrogen atom or a halogen atom is preferred, and a hydrogen atom is more preferred.

[0099] The C1-C10 alkyl group of R² is preferably a C1-C6 alkyl group.

[0100] The halogen atom of R² is preferably a fluorine atom, a chlorine atom or a bromine atom, but more preferably a fluorine atom or a chlorine atom.

[0101] The benzamide derivative represented by the formula (I) according to this invention is, for example, 2-amino-4-fluoro-5-(1-methyl-1H-imidazol-2-ylsulfanyl-N-thiazol-2-yl)benzamide, 2-amino-4-fluoro-5-(1-methyl-1H-imidazol-2-ylsulfanyl)-N-(4-methylthiazol-2-yl)benzamide, 2-amino-5-(1H-imidazol-2-ylsulfanyl)-N-(4-hydroxymethylthiazol-2-yl)benzamide, 2-amino-5-(1H-imidazol-2-ylsulfanyl)-N-(4-hydroxymethylthiazol-2-yl)benzamide, 2-amino-5-methylsulfanyl-N-thiazolo[5,4-b]pyridin-2-ylbenzamide, 2-amino-5-(4-methyl-4H-[1,2,4]triazol-3-ylsulfanyl)-N-(4-methylthiazol-2-yl)benzamide, 2-amino-5-(4H-[1,2,4]triazol-3-ylsulfanyl)-N-(4-methylthiazol-2-yl)benzamide, 2-amino-5-(5-methyl-4H-[1,2,4]triazol-3-ylsulfanyl)-N-[4-(1-methyl-1H-imidazol-2-ylsulfanylmethyl)thiazol-2-yl]benzamide, 2-amino-4-fluoro-5-(4-methyl-4H-[1,2,4]triazol-3-ylsulfanyl)-N-(4-methylthiazol-2-yl)benzamide, 2-amino-4-fluoro-5-(4,5-dimethyl-4H-[1,2,4]triazol-3-ylsulfanyl)-N-(4-methylthiazol-2-yl)benzamide, 2-amino-5-(2,5-dimethyl-2H-[1,2,4]triazol-3-ylsulfanyl)-N-(4-methylthiazol-2-yl)benzamide, 2-amino-4-fluoro-5-(4-methyl-4H-[1,2,4]triazol-3-ylsulfanyl)-N-(4-hydroxymethylthiazol-2-yl)benzamide, 2-amino-5-(4-methyl-4H-[1,2,4]triazol-3-ylsulfanyl)-N-(2-methylthiazol-4-yl)benzamide, 2-amino-5-(4-methyl-4H-[1,2,4]triazol-3-ylsulfanyl)-N-(4-methoxymethylthiazol-2-yl)benzamide, 2-amino-5-(4,5-dimethyl-4H-[1,2,4]triazol-3-ylsulfanyl)-N-(2-methylthiazol-4-yl)benzamide, 2-amino-4-fluoro-5-(4-methyl-4H-[1,2,4]triazol-3-ylsulfanyl)-N-(2-methylthiazol-4-yl)benzamide, 2-amino-5-(1-methyl-1H-imidazol-2-ylsulfanyl)-N-(4-methylthiazol-2-yl)benzamide, 2-amino-5-(4-methyl-4H-[1,2,4]triazol-3-ylsulfanyl)-N-thiazolo[5,4-b]pyridin-2-ylbenzamide, 2-amino-5-(1-methyl-1H-imidazol-2-ylsulfanyl)-N-thiazolo[5,4-b]pyridin-2-ylbenzamide, 2-amino-4-fluoro-5-(4-methyl-4H-[1,2,4]triazol-3-ylsulfanyl)-N-thiazolo[5,4-b]pyridin-2-ylbenzamide, 2-amino-5-(4,5-dimethyl-4H-[1,2,4]triazol-3-ylsulfanyl)-N-(4-methoxymethylthiazol-2-yl)benzamide, 2-amino-4-fluoro-5-(4,5-dimethyl-4H-[1,2,4]triazol-3-ylsulfanyl)-N-(4-methoxymethylthiazol-2-yl)benzamide, 2-amino-5-(thiazol-2-ylsulfanyl)-N-(4-methoxymethylthiazol-2-yl)benzamide, 2-amino-5-phenoxy-N-(4-methoxymethylthiazol-2-yl)benzamide, 2-amino-5-phenoxy-N-[4-(4-methyl-4H-[1,2,4]triazol-2-ylsulfanylmethyl)thiazol-2-yl]benzamide, 2-amino-5-(4-fluoro-2-methylsulfonylphenoxy)-N-(4-methylthiazol-2-yl)benzamide, 2-amino-5-(2-methylsulfonylphenoxy)-N-(2-methylthiazol-4-yl)benzamide or 2-amino-3-phenoxy-5-(2-methylsulfonylphenoxy)-N-(4-methylthiazol-2-yl)benzamide.

[0102] The benzamide derivative according to this invention can exist as a pharmaceutically acceptable salt. The salt concerned may be an acid addition salt or a base addition salt.

[0103] The acid addition salt is, for example, a hydrohalide salt such as a hydrochloride, hydrofluoride, hydrobromide or hydroiodide; an inorganic acid salt such as a nitrate, perchlorate, sulfate, phosphate or carbonate; a lower alkyl sulfonate such as a methanesulfonate, trifluoromethanesulfonate or ethanesulfonate; an arylsulfonate such as a benzenesulfonate or p-toluenesulfonate; an organic acid salt such as a fumarate, succinate, citrate, tartrate, oxalate or maleate; or an amino acid salt such as a glutamate or aspartate.

[0104] The base addition salt is, for example, an alkali metal salt of sodium or potassium, an alkaline earth metal salt of calcium or magnesium, an ammonium salt, or a salt of an organic base such as guanidine, triethylamine or dicyclohexylamine.

[0105] The compound of this invention may exist as a solvate, preferably a hydrate, of a free compound or its salt.

[0106] The compound according to this invention may contain a stereoisomer such as an optical isomer, a diastereomer or a geometric isomer, or a tautomer, depending on the type of substituent. It will be understood that all of these isomers are included in the compound according to this invention. It will further be understood that arbitrary mixtures of these isomers are also included in the compound according to this invention.

[0107] Since the compound of this invention has a glucokinase activation effect, it is useful as a therapeutic and/or prophylactic agent for diabetes, and as a prophylactic agent for complications of diabetes.

[0108] Herein, diabetic complications are illnesses occurring together with the symptoms of diabetes mellitus. Complications of diabetes mellitus include diabetic nephropathy, diabetic retinopathy, diabetic neuropathy and diabetic arteriosclerosis.

[0109] The compound according to this invention can be used both for IDDM (insulin-dependent diabetes mellitus) and NIDDM (non-insulin-dependent diabetes mellitus).

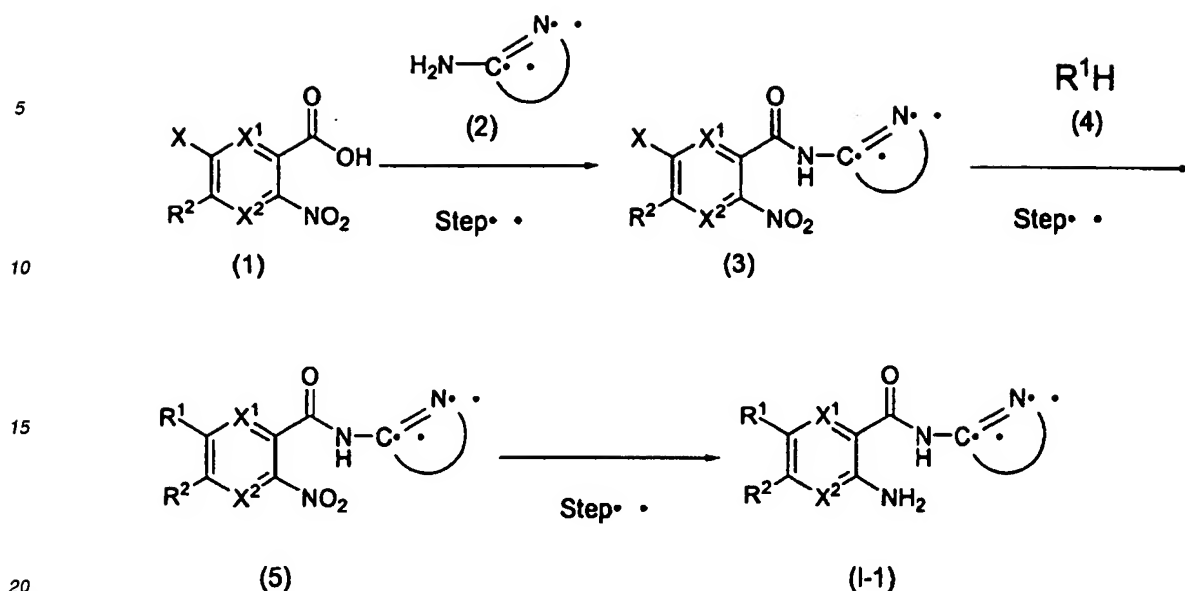
[0110] IDDM (insulin-dependent diabetes mellitus) results when insulin resistance due to obesity is added to a hereditary loss of insulin secretion and insulin resistance in skeletal muscle, and is considered to be mainly an adult disease. Insulin-dependent diabetes mellitus is classified as Type I or Type II depending on the factors.

[0111] The compound of this invention is considered to be useful not only in Type I insulin-dependent diabetes mellitus, but also in Type II diabetes mellitus wherein a sufficient fall of blood sugar level was impossible to attain with prior art antidiabetic agents.

[0112] In Type II diabetes mellitus, it is remarkable that hyperglycemia continues for a long time after taking food as compared with a healthy person, but the compound according to this invention is useful also in this Type II diabetes mellitus.

[0113] The method of manufacturing the compound of this invention will now be described.

[0114] The compound (I) of this invention can be easily manufactured according to reaction means known in the art, or by methods themselves known in the art. The compound having the general formula (I) of this invention can be manufactured not only by synthesis in the usual liquid phase, but also by a synthetic step using the solid phase, such as a combinatorial synthetic step or a parallel synthetic step, which has made remarkable progress in recent years. It is preferably manufactured by, for example, the following steps:



[the symbols in the formulae are as previously defined]

(Step 1)

[0115] This step is a method of reacting the carboxylic acid compound (1) or its reactant derivative with amino compound containing a monocyclic or bicyclic heteroaryl group which may be substituted by R^{10} represented by the aforesaid formula (II), or its salt, to manufacture the compound (3). This reaction may be carried out by the usual amide-forming reaction, using the method described in the literature (e.g., Theory and Experiment in Peptide Synthesis, Nobuo Izumiya et al, Maruzen, 1983; and Comprehensive Organic Synthesis, Vol. 6, Pergamon Press, 1991), a corresponding method, or a combination of these with the usual methods, i.e., using a condensation agent known in the art, or the ester activation method, the mixed anhydride method, the acid chloride method or the carbodiimide method, which can be used by those skilled in the art. The amide-forming reagent is, for example, thionyl chloride, N,N-dicyclohexylcarbodiimide, 1-methyl-2-bromopyridinium iodide, N,N'-carbonyldiimidazole, diphenylphosphoryl chloride, diphenylphosphoryl azide, N,N'-disuccinimidyl carbonate, N,N'-disuccinimidyl oxalate, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, ethyl chloroformate, isobutyl chloroformate or benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate. Among these, thionyl chloride, N,N-dicyclohexylcarbodiimide and benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate are preferred. In the amide forming reaction, a base or a condensation additive may be used together with the aforesaid amide forming reagent.

[0116] The base used is, for example, a tertiary aliphatic amine such as trimethylamine, triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, N-methylpyrrolidine, N-methylpiperidine, N,N-dimethylaniline, 1,8-diazabicyclo[5.4.0]undeca-7-ene (DBU) or 1,5-azabicyclo[4.3.0]nona-5-ene (DBN); or an aromatic amine such as pyridine, 4-dimethylaminopyridine, picoline, lutidine, quinoline or isoquinoline. Among these, tertiary aliphatic amines are preferred, and triethylamine or N,N-diisopropylethylamine is particularly preferred.

[0117] The condensation additive used is, for example, N-hydroxybenzotriazole hydrate, N-hydroxysuccinimide, N-hydroxy-5-norbornene-2,3-dicarboxyimide or 3-hydroxy-3, 4-dihydro-4-oxo-1,2,3-benzotriazole. Among these, N-hydroxybenzotriazole is particularly preferred.

[0118] The amount of the amino compound (2) used varies with the compounds used, the solvent and other reaction conditions, but it is usually 0.02 to 50 equivalents, and preferably 0.2 to 2 equivalents, relative to 1 equivalent of the carboxylic acid compound (1) or its reactive derivative. Herein, the reactive derivative is, for example, an active ester derivative or active amide derivative usually used in the field of organic chemistry.

[0119] The amount of the amide-forming reagent used varies with the compounds used, the solvent and other reaction conditions, but it is usually 1 to 50 equivalents, and preferably 1 to 5 equivalents, relative to 1 equivalent of the carboxylic acid compound (1) or its reactive derivative.

[0120] The amount of the condensation additive used varies with the compounds used, the solvent and other reaction conditions, but it is usually 1 to 50 equivalents, and preferably 1 to 5 equivalents, relative to 1 equivalent of the carboxylic acid compound (1) or its reactive derivative.

[0121] The amount of the base used varies with the compounds used, the solvent and other reaction conditions, but it is usually 1 to 50 equivalents, and preferably 3 to 5 equivalents.

[0122] The reaction solvent used in this step is, for example, an inert organic solvent and it is not particularly limited provided that it does not interfere with the reaction. Specific examples are methylene chloride, chloroform, 1,2-dichloroethane, trichloroethane, N,N-dimethylformamide, ethyl acetate, methyl acetate, acetonitrile, benzene, xylene, toluene, 1,4-dioxane, tetrahydrofuran, dimethoxyethane and a mixture of these solvents, but from the viewpoint of maintaining a suitable reaction temperature, methylene chloride, chloroform, 1,2-dichloroethane, acetonitrile, and N,N-dimethylformamide are particularly preferred.

[0123] The reaction temperature is -100°C to the boiling point of the solvent, but preferably 0°C to 30°C.

[0124] The reaction time is 0.5 to 96 hours, but preferably 3 to 24 hours.

[0125] The base, amide-forming reagent and condensation additive used in this step may each be of one kind, or a mixture of more than one kind.

[0126] If the compound (3) has a protecting group, this protecting group can be removed as required. The auxiliary group concerned can be removed by the method described in the literature (Protective Groups in Organic Synthesis, T.W.Green, 2nd edition, John Wiley & Sons, 1991), a corresponding method, or a combination thereof with an ordinary method.

[0127] The compound (3) thus obtained can be isolated and purified by a method known in the art, for example, concentration, concentration under reduced pressure, crystallization, solvent extraction, reprecipitation or chromatography, or it may not be isolated and purified, before proceeding to the next step.

(Step 2)

[0128] This step is a method of manufacturing the compound (5) by reacting the amide compound (3) obtained in the aforesaid Step 1 together with a compound (4).

[0129] In this reaction, a base may be added to the reaction system as required.

[0130] The compound (4) used is preferably a phenol derivative or a thiol derivative. The phenol derivative or thiol derivative is, for example, phenol, thiophenol, thioimidazole or thiotriazole.

[0131] The amount of the compound (4) used varies with the compounds used, the solvent and other reaction conditions, but it is usually 2 to 50 equivalents, and preferably 2 to 5 equivalents, relative to 1 equivalent of the amino derivative (3).

[0132] The base used may be a tertiary aliphatic amine such as trimethylamine, triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, N-methylpyrrolidine, N-methylpiperidine, N,N-dimethylaniline, 1,8-diazabicyclo[5.4.0]undeca-7-ene (DBU) or 1,5-azabicyclo[4.3.0]nona-5-ene (DBN); an aromatic amine such as pyridine, 4-dimethylaminopyridine, picoline, lutidine, quinoline or isoquinoline; an alkali metal such as metallic potassium, metallic sodium or metallic lithium; an alkali metal hydride such as sodium hydride or potassium hydride; an alkyl derivative of an alkali metal such as butyllithium; an alkali metal alkoxide such as potassium tert-butyrate, sodium ethylate or sodium methylate; an alkali metal hydroxide such as potassium hydroxide or sodium hydroxide; or an alkali metal carbonate such as potassium carbonate. Among these, tertiary aliphatic amines, alkali metal hydrides or alkali metal carbonates are preferred, and triethylamine, N,N-diisopropylethylamine, sodium hydride or potassium carbonate is particularly preferred.

[0133] The amount of the base used varies with the compounds used, the solvent and other reaction conditions, but it is usually 0 to 50 equivalents, and preferably 2 to 10 equivalents, relative to 1 equivalent of the amide compound (3). One, two or more kinds of bases may be used if required.

[0134] The inert organic solvent used is not particularly limited provided that it does not interfere with the reaction, but specific examples are methylene chloride, chloroform, 1,2-dichloroethane, trichloroethane, N,N-dimethylformamide, N,N-dimethylacetamide, ethyl acetate, methyl acetate, acetonitrile, benzene, xylene, water, toluene, 1,4-dioxane, tetrahydrofuran, and a mixture of these solvents.

[0135] The compound (5) thus obtained can be isolated and purified by a method known in the art, for example, concentration, concentration under reduced pressure, crystallization, solvent extraction, reprecipitation or chromatography.

(Step 3)

[0136] This step is the method of manufacturing the compound (I-1) of this invention by reducing the compound (5). The reduction reaction used in this step may be a method known by persons skilled in the art. Specifically, the reduction reaction used in this step is, for example, (1) catalytic reduction using hydrogen, formic acid, ammonium formate or hydrazine hydrate, and a palladium, platinum or nickel catalyst, (2) reduction using hydrochloric acid or ammonium chloride, and iron, or (3) reduction using methanol and tin chloride.

[0137] The amount of the reducing agent used in the aforesaid reducing reaction varies with the compounds used,

the solvent and other reaction conditions, but it is usually 1 to 50 equivalents, and preferably 2 to 20 equivalents, relative to 1 equivalent of the compound (5).

[0138] The reaction solvent used is not particularly limited provided that it does not interfere with the reaction. Examples are a halogenated hydrocarbon such as dichloromethane or chloroform, an ether such as diethyl ether, tert-butyl methyl ether or tetrahydrofuran, an amide such as N,N-dimethylformamide or N,N-dimethylacetamide, a sulfoxide such as dimethyl sulfoxide, a nitrile such as acetonitrile, an alcohol such as methanol, ethanol or propanol, an aromatic hydrocarbon such as benzene, toluene or xylene, water, and a mixture of these solvents.

[0139] The reaction temperature and reaction time are not particularly limited, but the reaction may be performed at -10°C to 100°C, preferably 0°C to 50°C, for 1 to 20 hours, preferably 1 to 5 hours.

[0140] The compound (I-1) thus obtained can be isolated and purified by a method known in the art, for example, concentration, concentration under reduced pressure, crystallization, solvent extraction, reprecipitation or chromatography, or it may not be isolated and purified, before proceeding to the next step.

[0141] The compounds of the aforesaid steps may have a protecting group on each substituent. This protecting group in each step may be removed by a method known in the art, a corresponding method, or a combination of these methods with conventional methods. Various removal reactions are possible depending on the compounds, type of reaction and other reaction conditions, and the protecting groups can be removed individually or simultaneously, as decided by a person skilled in the art. The protecting group is for, for example, hydroxyl, amino, carboxyl, aldehyde or keto. The removal order of the protecting groups is not particularly limited.

[0142] The protecting group for hydroxyl is, for example, a lower alkyl silyl group such as tert-butyl dimethylsilyl or tert-butyl diphenylsilyl, a lower alkoxymethyl group such as methoxymethyl or 2-methoxyethoxymethyl, an aralkyl group such as benzyl or p-methoxybenzyl, or an acyl group such as formyl or acetyl. Among these, tert-butyl dimethylsilyl and acetyl are preferred.

[0143] The protecting group for amino is, for example, an aralkyl group such as benzyl or p-nitrobenzyl, an acyl group such as formyl or acetyl, a lower alkoxycarbonyl group such as ethoxycarbonyl or tert-butoxycarbonyl, or an aralkyloxycarbonyl group such as benzyloxycarbonyl or p-nitrobenzyloxycarbonyl. Among these, nitrobenzyl, tert-butoxycarbonyl and benzyloxycarbonyl are preferred.

[0144] The protecting group for carboxyl is, for example, a lower alkyl group such as methyl, ethyl or tert-butyl, or an aralkyl group such as benzyl or p-methoxybenzyl. Among these, methyl, ethyl, tert-butyl and benzyl are preferred.

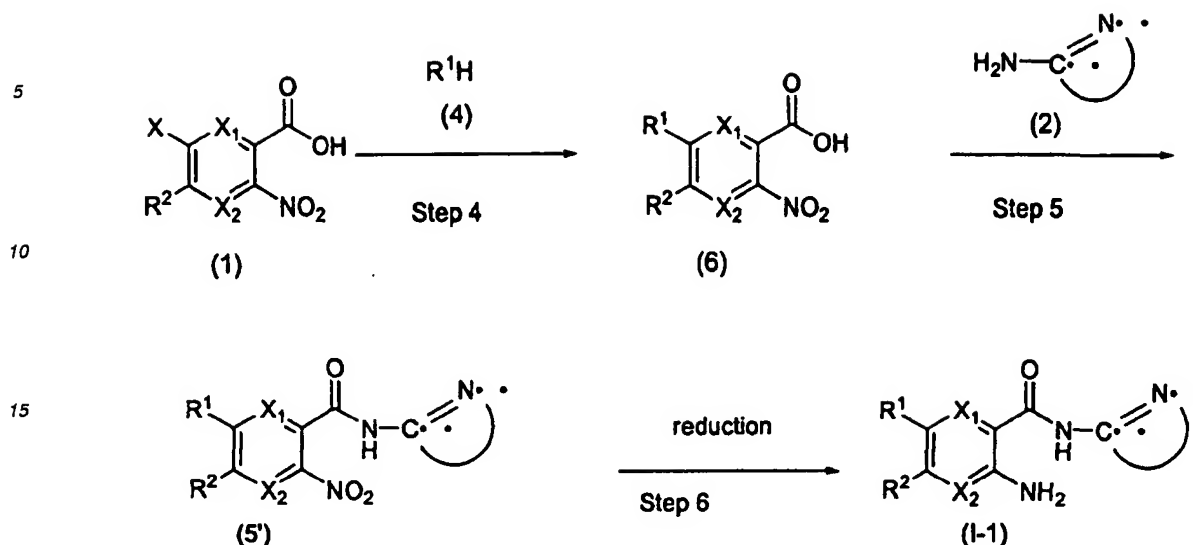
[0145] The protecting group for keto is, for example, dimethyl ketal, 1,3-dioxirane, 1,3-dioxolane, 1,3-dithian or 1,3-dithiolane. Among these, dimethyl ketal and 1,3-dioxolane are more preferred.

[0146] The protecting group for aldehyde may be dimethyl acetal, 1,3-dioxirane, 1,3-dioxolane, 1,3-dithian or 1,3-dithiolane. Among these, dimethyl acetal and 1,3-dioxolane are more preferred.

[0147] In manufacturing the compound of this invention, the protecting group may be introduced into a functional group in order to make the reaction proceed efficiently. These protecting groups can be suitably chosen by a person skilled in the art, and the protecting group can be removed by the method described in "Protective groups in Organic Synthesis", a corresponding method, or a combination thereof with an ordinary method. The removal order of the protecting groups may be decided by a person skilled in the art.

[0148] The compound (I-1) thus obtained can be isolated and purified by a method known in the art, for example, concentration, concentration under reduced pressure, crystallization, reprecipitation, solvent extraction or chromatography, or it may not be isolated and purified, before proceeding to the next step.

[0149] The compound (I-1) of this invention may also be manufactured by the following steps:



[the symbols in the formulae are as previously defined]

[0150] In the aforesaid Step 4, Step 5 and Step 6, the amount of reagent, reaction solvent, reaction temperature and other reaction conditions may be identical to those of the aforesaid Step 2, Step 1 and Step 3.

[0151] When a protecting group is required on R^2 , a person skilled in the art may suitably select the protecting group by the method described in "Protective Groups in Organic Synthesis", a corresponding method, or a combination thereof with an ordinary method.

[0152] The compound (6) or (5') thus obtained can be isolated and purified by a method known in the art, for example, concentration, concentration under reduced pressure, crystallization, reprecipitation or solvent extraction, or it may not be isolated and purified, before proceeding to the next step.

[0153] The compound (I-1) of this invention can be isolated and purified by a method known in the art, for example, concentration, concentration under reduced pressure, crystallization, reprecipitation or solvent extraction.

[0154] In the aforesaid Steps 1 to 6, the removal of the protecting group is different depending on the type of protecting group and stability of the compound, and it may be performed by the method described in "Protective Groups in Organic Synthesis" (T.W.Green, 2nd edition, John Wiley & Sons, 1991), a corresponding method, or a combination thereof with an ordinary method. For example, this may be performed by solvolysis using an acid or a base, chemical reduction using a hydrogenated metal complex, or catalytic reduction using a palladium charcoal catalyst or Raney nickel catalyst.

[0155] The benzamide compound provided by this invention can exist as a pharmaceutically acceptable salt. This salt is described in formula (I) and "Embodiments of the Invention."

[0156] The salt can be manufactured by the usual methods using the compound represented by formula (I-1). Specifically, when the compound in the aforesaid (I) and (I-1) has a basic group derived, for example, from an amino group or a pyridyl group in the molecule, it can be converted to the corresponding pharmaceutically acceptable salt by treating this compound with an acid.

[0157] The acid addition salt is, for example, a hydrohalide salt such as a hydrochloride, hydrofluoride, hydrobromide or hydroiodide; an inorganic acid salt such as a nitrate, perchlorate, sulfate, phosphate or carbonate; a lower alkyl sulfonate such as a methanesulfonate, trifluoromethanesulfonate or ethanesulfonate; an arylsulfonate such as a benzenesulfonate or p-toluenesulfonate; an organic acid salt such as a fumarate, succinate, citrate, tartrate, oxalate or maleate; or an amino acid salt such as a glutamate or aspartate.

[0158] If the compound of this invention has an acidic group such as carboxyl in this group, it may be converted to the corresponding pharmaceutically acceptable salt by treating this compound with a base.

[0159] The base addition salt is, for example, an alkali metal salt of sodium or potassium, an alkaline earth metal salt of calcium or magnesium, an ammonium salt, or a salt of an organic base such as guanidine, triethylamine or dicyclohexylamine. The compound of this invention may exist as a hydrate or solvate of a free compound or its salt.

[0160] Next, the glucokinase activation effect of the compound according to this invention represented by the general formula (I), the accompanying hypoglycemic action and its test method, will be described.

[0161] The measurement of the outstanding glucokinase activation effect of the compound represented by the general formula (I) may be performed by the method described in the literature (e.g., Diabetes, Vol. 45, pp. 1671-1677, 1996), or a corresponding method.

[0162] The degree of glucokinase activity is investigated not by measuring glucose-6-phosphate directly, but by

measuring the amount of Thio-NADH produced when glucose-6-phosphate dehydrogenase, which is a reporter enzyme, generates phosphogluconolactone from glucose-6-phosphate.

[0163] The recombinant human liver GK used for this assay was expressed by E.coli as a FLAG fusion protein, and was purified by ANTIFLAG M2 AFFINITY GEL (Sigma).

[0164] The assay was performed at 30°C using flat bottom 96-well plate. 69 µl of Assay buffer (25 mM Hepes Buffer: pH=7.2, 2 mM MgCl₂, 1 mM ATP, 0.5 mM TNAD, 1 mM dithiothreitol) was pipetted, and 1 µl of a DMSO solution of the compound was added, or 1 µl of DMSO as a control. Next, 20 µl of Enzyme mixture (FLAG-GK, 20 U/ml G6PDH) which had been cooled in ice was pipetted, and 10 µl of 25 mM glucose which is the substrate was added to start the reaction (final glucose concentration = 2.5 mM).

[0165] After starting the reaction, the increase of absorbance at 405 nm was measured for 10 minutes every 30 seconds, and the compound was evaluated using the increase for the first 5 minutes. FLAG-GK was added so that the absorbance increase after 5 minutes in the presence of 1% DMSO ranged from 0.05 to 0.1.

[0166] As a number indicating the GK activity of the compound, AC200 was used. The definition of AC200 is the concentration of compound required to increase the OD value by 2 times (to 200%), taking the OD value of the DMSO control as 100%.

[0167] When GK activation ability was measured using the AC200 value as an index of GK activation ability, the compounds shown in the following manufacturing examples showed 200% activity at 10 µM or less.

[0168] Next, the fact that the compound of this invention represented by the general formula (I) having the aforesaid GK activation effect has an excellent hypoglycemic action, was confirmed, for example, by the following test method.

[0169] To demonstrate the specific hypoglycemic action of the compound in this invention, the compound of Manufacturing Example 33 included in this invention was selected, and its hypoglycemic action was investigated. The effect on blood sugar level when this compound was administered after sugar loading was investigated using the mouse. The test method and test result are shown below.

(Test method)

[0170] A male ICR mouse (8-11th week, n=5) bred under free food intake and water intake conditions, was denied food from the night before the test, and the tip of the tail was cut off slightly with scissors to take blood. The compound suspended in 0.5% methyl cellulose solution wherein glucose was dissolved was then administered orally. As a control, 0.5% methyl cellulose solution wherein glucose had been dissolved, was administered orally to the rat. Blood was collected every 30 minutes after administration of the test drug, and plasma was separated from the obtained blood by centrifugal separation. The blood sugar level in the plasma was assayed by the glucose oxidase method using a commercial test reagent (Detamina GL-E (Kyowa Medex)). The insulin concentration in the plasma was assayed by enzyme immunoassay using a commercial measurement kit (Morinaga Bioscience Laboratory). The obtained numerical values were analyzed by Student's t-test, and the statistical significant difference was computed. The result is shown in the following Table 1.

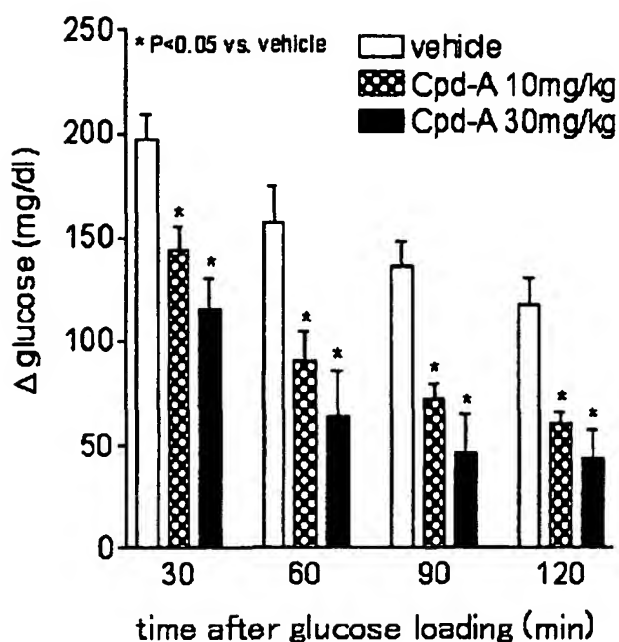
{Table 1}

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[0171] In the above (Table 1), Cpd-A shows the compound mentioned in Manufacturing Example 33 below.

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[0172] In addition to the aforesaid method, the hypoglycemic action of the compound of this invention can be measured also by the method described in the literature (Proc. Natl. Acad. Sci., 92:3096-3099, 1995), a corresponding method, or a combination of these with an ordinary test method.

30

[0173] Using the AC200 value as an index of the GK activation ability of the compound, the compounds of Manufacturing Examples 1 to 117 all showed 200% activity at 10 μ M or less. Therefore, the compound according to this invention is useful as a medication for diabetic therapy and/or prevention.

[0174] From the above results, as the benzamide derivative represented by the general formula (I) shows a hypoglycemic action by activating glucokinase, it is useful as a diabetes treatment and/or diabetes prophylactic agent, or as a prophylactic agent for diabetic complications such as diabetic retinopathy, diabetic nephropathy, diabetic arteriosclerosis and diabetic ischemic heart disease.

35

[0175] Since the compound represented by the general formula (I) according to this invention has a glucokinase activation effect, it is useful not only in insulin-dependent diabetes mellitus, but also in non-insulin-dependent diabetes mellitus.

40

[0176] The novel aminobenzamide derivative represented by the formula (I) may be administered orally or parenterally. In using the compound according to this invention in clinical practice, pharmaceutically permitted additives can be added to manufacture various preparations depending on the mode of administration. Various kinds of additives usually used in the pharmaceutical preparation field may then be used. Examples are gelatin, lactose, white soft sugar, titanium oxide, starch, crystalline cellulose, hydroxypropylmethylcellulose, carboxymethylcellulose, corn starch, microcrystalline wax, white vaseline, magnesium aluminometasilicate, calcium phosphate anhydrous, citric acid, trisodium citrate, hydroxypropylcellulose, sorbitol, sorbitan fatty acid ester, polysorbate, sucrose fatty acid ester, polyoxyethylene hydrogenated castor oil, polyvinylpyrrolidone, magnesium stearate, light silicic anhydride, talc, vegetable oil, benzyl alcohol, gum arabic, propylene glycol, polyalkylene glycol, cyclodextrin and hydroxypropylcyclodextrin.

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[0177] The mixture with these additives may be made into various pharmaceutical preparations, i.e., solid preparations such as tablets, capsules, granules, powders or suppositories; or liquid preparations such as syrups, elixirs or injections. These can be prepared according to the usual method in the field of pharmaceutical preparation. When making up liquid preparations, the compound may, if necessary, be dissolved or suspended in water or another suitable solvent. In the case of injections, it may be dissolved or suspended in physiological saline or glucose solution as required, and buffers and preservatives may further be added.

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[0178] These pharmaceutical preparations can contain the compound of this invention 1.0 to 100 wt%, preferably 1.0 to 60 wt%.

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[0179] When the compound according to this invention is used in clinical practice, for example, the dosage and frequency of administration vary with the patient's sex, age, weight, condition, and the kind and extent of results desired, but preferably for an adult, in the case of oral administration, 0.1 to 100 mg/kg is administered one to several times per day, and in the case of parenteral administration, 0.001 to 10 mg/kg is administered one to several times per day.

Best Modes for Carrying Out the Invention

[0180] The present invention will now be explained in greater detail through Formulation Examples and Manufacturing Examples, with the understanding that the invention is in no way limited to these examples.

Formulation Example 1

[0181] Ten parts of the compound of Manufacturing Example 1, 15 parts of heavy magnesium oxide and 75 parts of lactose were uniformly mixed to prepare pulverulent or finely-granular powders with sizes of no greater than 350 μm . The powders were placed in capsule containers to prepare capsules.

Formulation Example 2

[0182] Forty-five parts of the compound of Manufacturing Example 1, 15 parts of starch, 16 parts of lactose, 21 parts of crystalline cellulose, 3 parts of polyvinyl alcohol and 30 parts of distilled water were uniformly mixed, and the mixture was subsequently crushed, granulated and dried, and then filtered to prepare granules with diameters of 1410 to 177 μm .

Formulation Example 3

[0183] After preparing granules by the same method as in Formulation Example 2, 3 parts of calcium stearate was added to 96 parts of the granules, and the mixture was compressed and molded to form tablets with diameters of 10 mm.

Formulation Example 4

[0184] Ten parts of crystalline cellulose and 3 parts of calcium stearate were added to 90 parts of the granules obtained by the method in Formulation Example 2, and the mixture was compressed and molded to form tablets with diameters of 8 mm. Then a mixed suspension of syrup gelatin and sedimentary calcium carbonate was added to prepare sugar-coated tablets.

[0185] The present invention will now be explained in greater detail through Manufacturing Examples and Reference Examples, with the understanding that the invention is in no way limited to these examples.

[0186] The thin-layer chromatography carried out in the examples employed Silicagel 60F₂₄₅ (Merck) as the plate and a UV detector as the detector. The column silica gel used was Wakogel™ C-300 (Wako Pure Chemical Industries), and the reverse-phase column silica gel used was LC-SORB™ SP-B-ODS (Chemco) or YMC-GEL™ ODS-AQ 120-S50 (Yamamura Chemicals Lab).

[0187] The abbreviations in the examples are explained below.

i-Bu: isobutyl

n-Bu: n-butyl

t-Bu: t-butyl

Me: methyl

Et: ethyl

Ph: phenyl

i-Pr: isopropyl

n-Pr: n-propyl

CDCl₃: heavy chloroform

CD₃OD: heavy methanol

DMSO-d₆: heavy dimethylsulfoxide

[0188] The abbreviations for the nuclear magnetic resonance spectra are explained below.

s : singlet

d : doublet

dd: double doublet

t : triplet

m : multiplet

br: broad

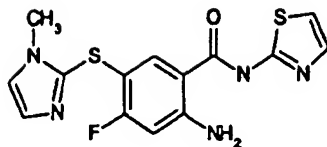
q : quartet

J : coupling constant

Hz: Hertz

Manufacturing Example 1

[0189]



Preparation of 2-amino-4-fluoro-5-(1-methyl-1H-imidazol-2-ylsulfanyl)-N-thiazol-2-ylbenzamide

[0190] Two drops of N,N-dimethylformamide and 0.51 ml (5.91 mmol) of oxalyl chloride were dripped into a methylene chloride solution (20 ml) of 1.00 g (4.92 mmol) of 4,5-difluoro-2-nitrobenzoic acid on ice, and after the addition was completed, the reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure, and an acid chloride was obtained as a colorless oily material.

[0191] 0.91 ml (9.84 mmol) of pyridine was added to a methylene chloride solution (10 ml) of 493 mg (4.92 mmol) of 2-aminothiazole, the methylene chloride solution (5 ml) of the acid chloride previously obtained was dripped in on ice, and after the addition was completed, the reaction mixture was stirred at room temperature overnight. An aqueous solution of 1 N hydrochloric acid was added to the reaction mixture, the mixture was extracted with chloroform, and then the organic layer was washed with water, an aqueous solution of saturated sodium bicarbonate and saturated brine solution, dried, and concentrated under reduced pressure. The obtained residue was recrystallized from chloroform, and 923 mg of an amide was obtained as a light yellow solid (yield: 66%).

[0192] 1.35 ml (9.68 mmol) of triethylamine and 443 mg (3.87 mmol) of 1-methyl-2-mercaptimidazole were added to an acetonitrile solution (10.0 ml) of 920 mg (3.23 mmol) of the obtained amide, and the reaction mixture was heated under reflux overnight. The reaction mixture was concentrated under reduced pressure, the obtained residue was recrystallized from methanol, and 552 mg of a nitro compound was obtained as a yellow solid (yield: 45%).

[0193] 2.4 g of iron powder was added to a mixture of an isopropanol solution (20 ml) of 480 mg (1.27 mmol) of the obtained nitro compound and an aqueous solution (2 ml) of saturated ammonium chloride, and heated under reflux for 30 minutes. After cerite filtration, the reaction mixture was concentrated under reduced pressure, and the obtained residue was purified by silica gel column chromatography (chloroform:methanol=8:1) to obtain 270 mg of the title compound as white crystals (yield: 55%).

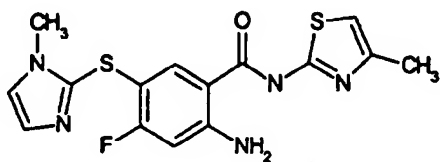
¹HNMR (CD₃OD) δ: 3.79 (3H, s), 6.51 (1H, d, J=11.4Hz), 6.62 (1H, d, J=1.0Hz), 7.00 (1H, d, J=1.3Hz), 7.17 (1H, d, J=1.3Hz), 8.04 (1H, d, J=8.0Hz)

ESI-MS(m/e): 350[M+H]⁺

[0194] The compounds of Manufacturing Examples 2 to 82 were obtained by the same method as in Manufacturing Example 1. Analytical data for compounds of representative manufacturing examples are given below.

Manufacturing Example 2

[0195]



Preparation of 2-amino-4-fluoro-5-(1-methyl-1H-imidazol-2-ylsulfanyl)-N-(4-methylthiazol-2-yl)benzamide

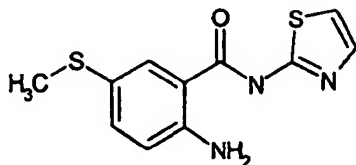
[0196] ¹HNMR(CD₃OD) δ: 2.33 (3H, d, J=1.0Hz), 3.79 (3H, s), 6.51 (1H, d, J=11.4Hz), 6.62 (1H, d, J=1.0Hz), 7.00

(1H, d, J=1.3Hz), 7.17 (1H, d, J=1.3Hz), 8.04 (1H, d, J=8.0Hz)

FAB-MS(m/e): 364[M+H]⁺

Manufacturing Example 3

[0197]



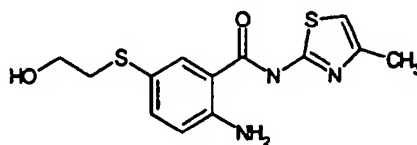
Preparation of 2-amino-5-methylsulfanyl-N-thiazol-2-ylbenzamide

[0198] ¹HNMR(CDCl₃) δ: 2.39 (3H, s), 6.72 (1H, d, J=8.5Hz), 6.97 (1H, d, J=3.6Hz), 7.30-7.37 (2H, m), 7.65 (1H, d, J=3.0Hz)

FAB-MS(m/e): 266 [M+H]⁺

Manufacturing Example 4

[0199]



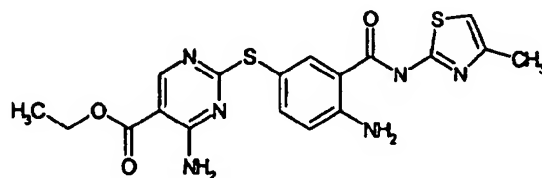
Preparation of 2-amino-5-(2-hydroxyethanesulfanyl)-N-(4-methylthiazol-2-yl)benzamide

[0200] ¹HNMR(CD₃OD) δ: 2.30 (3H, d, J=1.1Hz), 2.91 (2H, t, J=6.9Hz), 3.63 (2H, t, J=6.9Hz), 6.64 (1H, d, J=1.1Hz), 6.76 (1H, d, J=8.6Hz), 7.37 (1H, dd, J=2.1Hz, 8.6Hz), 7.84 (1H, d, J=2.1Hz)

FAB-MS(m/e): 310[M+H]⁺

Manufacturing Example 5

[0201]



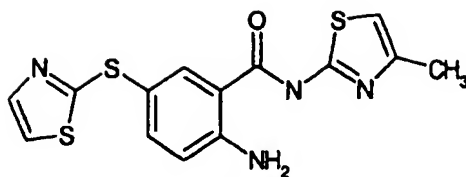
Preparation of 2-amino-5-(4-amino-5-ethoxycarbonylpyrimidin-2-ylsulfanyl)-N-(4-methylthiazol-2-yl)benzamide

[0202] ¹HNMR (CD₃OD) δ: 1.34 (3H, t, J=7.2Hz), 2.31 (3H, d, J=1.0Hz), 4.32 (2H, q, J=7.2Hz), 6.63 (1H, s), 6.85 (1H, d, J=8.7Hz), 7.38 (1H, dd, J=2.2Hz, 8.7Hz), 7.94 (1H, d, J=2.2Hz), 8.55 (1H, s)

FAB-MS(m/e): 431[M+H]⁺

Manufacturing Example 6

[0203]

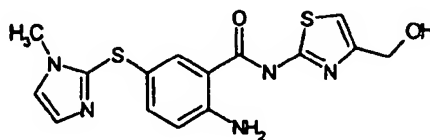


Preparation of 2-amino-5-(thiazol-2-ylsulfanyl)-N-(4-methylthiazol-2-yl)benzamide

[0204] $^1\text{H NMR}(\text{CD}_3\text{OD})$ δ : 2.31 (1H, d, $J=1.0\text{Hz}$), 6.63 (1H, s), 6.88 (1H, d, $J=8.7\text{Hz}$), 7.38 (1H, d, $J=3.0\text{Hz}$), 7.48 (1H, dd, $J=2.1\text{Hz}$, 8.7Hz), 7.62 (1H, d, $J=3.0\text{Hz}$), 8.13 (1H, d, $J=2.1\text{Hz}$)
 FAB-MS(m/e): 349 $[\text{M}+\text{H}]^+$

Manufacturing Example 7

[0205]

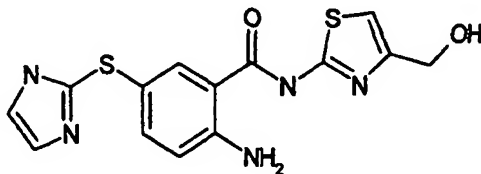


Preparation of 2-amino-5-(1-methyl-1H-imidazol-2-ylsulfanyl)-N-(4-hydroxymethylthiazol-2-yl)benzamide

[0206] $^1\text{H NMR}(\text{DMSO}-d_6)$ δ : 3.64 (3H, s), 4.49 (2H, d, $J=6.0\text{Hz}$), 5.24 (1H, t, $J=6.0\text{Hz}$), 6.74 (1H, d, $J=8.8\text{Hz}$), 6.93 (1H, s), 6.94 (1H, s), 7.16 (1H, dd, $J=1.6\text{Hz}$, 8.8Hz), 7.29 (1H, s), 7.99 (1H, d, $J=1.6\text{Hz}$)
 FAB-MS(m/e): 362 $[\text{M}+\text{H}]^+$

Manufacturing Example 8

[0207]

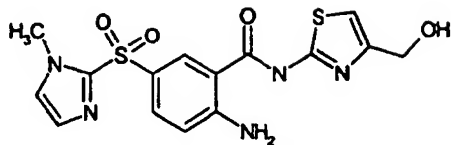


Preparation of 2-amino-5-(1H-imidazol-2-ylsulfanyl)-N-(4-hydroxymethylthiazol-2-yl)benzamide

[0208] $^1\text{H NMR}(\text{DMSO}-d_6)$ δ : 4.48 (2H, s), 5.22 (1H, br), 6.74 (1H, d, $J=8.8\text{Hz}$), 6.92 (2H, s), 7.17 (1H, s), 7.23 (1H, d, $J=8.8\text{Hz}$), 8.05 (1H, s)
 FAB-MS(m/e): 348 $[\text{M}+\text{H}]^+$

Manufacturing Example 9

[0209]

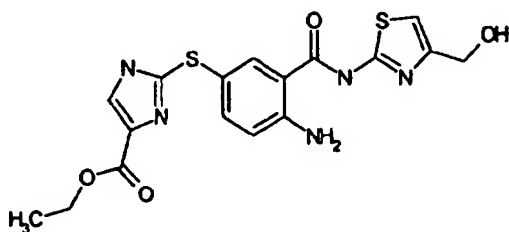


Preparation of 2-amino-5-(1-methyl-1H-imidazol-2-ylsulfonyl)-N-(4-hydroxymethylthiazol-2-yl)benzamide

[0210] $^1\text{H NMR}$ (DMSO- d_6) δ : 3.88 (3H, s), 4.46 (2H, s), 5.25 (1H, br), 6.87 (1H, d, $J=8.4\text{Hz}$), 6.90 (1H, s), 7.02 (1H, s), 7.40 (1H, s), 7.52 (1H, s), 7.62 (1H, d, $J=8.4\text{Hz}$)
 FAB-MS(m/e): 394[$M+H$] $^+$

Manufacturing Example 10

[0211]

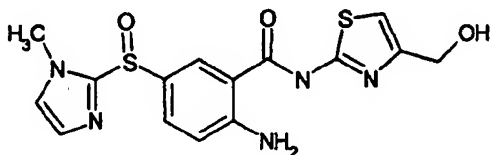


Preparation of 2-amino-5-(4-ethoxycarbonyl-1H-imidazol-2-ylsulfanyl)-N-(4-hydroxymethylthiazol-2-yl)benzamide

[0212] $^1\text{H NMR}$ (CD_3OD) δ : 1.33 (3H, t, $J=7.1\text{Hz}$), 4.29 (2H, q, $J=7.1\text{Hz}$), 4.60 (2H, d, $J=0.9\text{Hz}$), 6.79 (1H, d, $J=8.7\text{Hz}$), 6.93 (1H, d, $J=0.9\text{Hz}$), 7.39 (1H, dd, $J=2.1\text{Hz}$, 8.7Hz), 7.68-7.69 (1H, m), 8.00 (1H, d, $J=2.1\text{Hz}$)
 FAB-MS(m/e): 420[$M+H$] $^+$

Manufacturing Example 11

[0213]

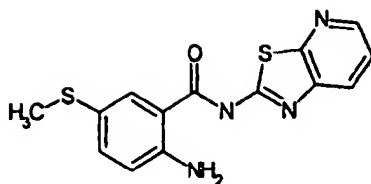


Preparation of 2-amino-5-(1-methyl-1H-imidazol-2-ylsulfinyl)-N-(4-hydroxymethylthiazol-2-yl)benzamide

[0214] $^1\text{H NMR}$ (DMSO- d_6) δ : 3.70 (3H, s), 4.46 (2H, s), 5.21 (1H, br), 6.88 (1H, s), 6.89 (1H, d, $J=8.8\text{Hz}$), 7.03 (1H, s), 7.35 (1H, s), 7.38 (1H, d, $J=8.8\text{Hz}$), 8.14 (1H, s)
 FAB-MS(m/e): 378[$M+H$] $^+$

Manufacturing Example 12

[0215]



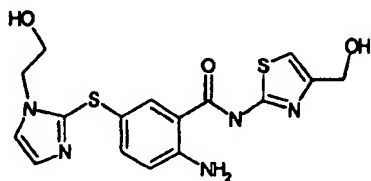
Preparation of 2-amino-5-methylsulfanyl-N-thiazolo[5,4-b]pyridin-2-ylbenzamide

[0216] $^1\text{H NMR}(\text{CDCl}_3)$ δ : 2.39 (3H, s), 5.84 (2H, br), 6.74 (1H, d, $J=8.4\text{Hz}$), 7.34 (1H, d, $J=4.8\text{Hz}$), 7.38 (1H, dd, $J=2.0\text{Hz}$, 8.4Hz), 7.61 (1H, d, $J=2.0\text{Hz}$), 7.89 (1H, dd, $J=1.2\text{Hz}$, 8.4Hz), 8.81 (1H, dd, $J=1.2\text{Hz}$, 4.8Hz)

FAB-MS(m/e): 317 $[\text{M}+\text{H}]^+$

Manufacturing Example 13

[0217]



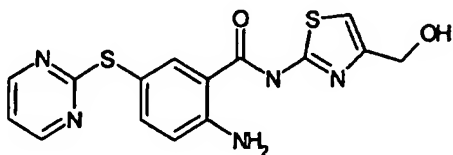
Preparation of 2-amino-5-(1-hydroxyethyl-1H-imidazol-2-ylsulfanyl)-N-(4-hydroxymethylthiazol-2-yl)benzamide

[0218] $^1\text{H NMR}(\text{CD}_3\text{OD})$ δ : 3.73 (2H, t, $J=4.8\text{Hz}$), 4.27 (2H, t, $J=4.8\text{Hz}$), 4.61 (2H, s), 6.74 (1H, d, $J=8.8\text{Hz}$), 6.93 (1H, s), 7.04 (1H, s), 7.27-7.30 (2H, m), 7.89 (1H, s)

FAB-MS(m/e): 392 $[\text{M}+\text{H}]^+$

Manufacturing Example 14

[0219]



Preparation of 2-amino-5-(pyrimidin-2-ylsulfanyl)-N-(4-hydroxymethylthiazol-2-yl)benzamide

[0220] $^1\text{H NMR}(\text{CDCl}_3)$ δ : 4.44 (2H, d, $J=5.2\text{Hz}$), 5.18 (1H, t, $J=5.2\text{Hz}$), 6.81 (1H, d, $J=8.4\text{Hz}$), 6.87 (1H, s), 7.04 (2H, br), 7.16 (1H, d, $J=8.8\text{Hz}$), 7.32 (1H, d, $J=8.8\text{Hz}$), 8.13 (1H, s), 8.84 (2H, d, $J=8.4\text{Hz}$)

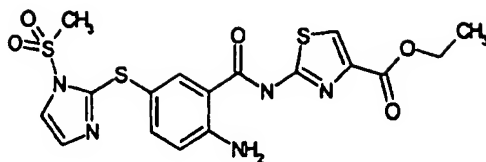
FAB-MS(m/e): 360 $[\text{M}+\text{H}]^+$

Manufacturing Example 15

[0221]

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Preparation of 2-amino-5-(1-methanesulfonyl-1H-imidazol-2-ylsulfanyl)-N-(4-ethoxycarbonylthiazol-2-yl)benzamide

15

[0222] $^1\text{H NMR}(\text{CDCl}_3)$ δ : 1.31 (3H, t, $J=7.2\text{Hz}$), 3.41 (3H, s), 4.30 (2H, q, $J=7.2\text{Hz}$), 6.69 (1H, d, $J=8.4\text{Hz}$), 6.88 (1H, d, $J=2.0\text{Hz}$), 7.32 (1H, d, $J=2.06\text{Hz}$), 7.40 (1H, dd, $J=2.0\text{Hz}$, 8.4Hz), 7.74 (1H, s), 7.95 (1H, d, $J=2.0\text{Hz}$)

FAB-MS(m/e): 468 $[\text{M}+\text{H}]^+$

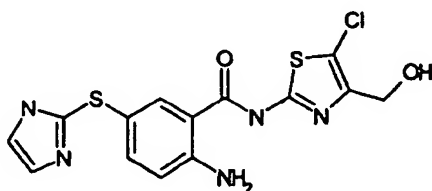
Manufacturing Example 16

20

[0223]

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Preparation of 2-amino-5-(1H-imidazol-2-ylsulfanyl)-N-(4-hydroxymethyl-5-chlorothiazol-2-yl)benzamide

35

[0224] $^1\text{H NMR}(\text{CD}_3\text{OD})$ δ : 4.56 (2H, s), 6.76 (1H, d, $J=8.8\text{Hz}$), 7.05 (2H, s), 7.34 (1H, dd, $J=2.0\text{Hz}$, 8.8Hz), 7.95 (1H, d, $J=2.0\text{Hz}$)

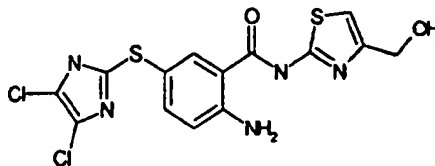
FAB-MS(m/e): 382 $[\text{M}+\text{H}]^+$

Manufacturing Example 17

40

[0225]

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Preparation of 2-amino-5-(4,5-dichloro-1H-imidazol-2-ylsulfanyl)-N-(4-hydroxymethylthiazol-2-yl)benzamide

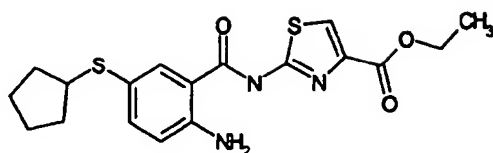
[0226] $^1\text{H NMR}(\text{CD}_3\text{OD})$ δ : 4.60 (2H, s), 6.79 (1H, d, $J=2.0\text{Hz}$), 6.93 (1H, s), 7.37 (1H, dd, $J=2.0\text{Hz}$, 8.8Hz), 7.95 (1H, d, $J=2.0\text{Hz}$)

FAB-MS(m/e): 416 $[\text{M}+\text{H}]^+$

55

Manufacturing Example 18

[0227]

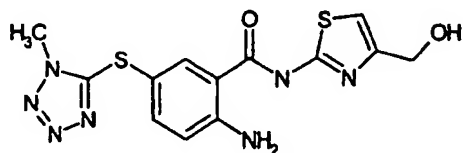


Preparation of 2-amino-5-cyclopentylsulfanyl-N-(4-ethoxycarbonylthiazol-2-yl)benzamide

[0228] $^1\text{H NMR}(\text{CDCl}_3)$ δ : 1.35 (3H, t, $J=6.0\text{Hz}$), 1.49-1.92 (8H, m), 3.29-3.33 (1H, m), 4.34 (2H, q, $J=6.0\text{Hz}$), 5.89 (2H, s), 6.66 (1H, d, $J=8.8\text{Hz}$), 7.38 (1H, dd, $J=2.0\text{Hz}$, 8.8Hz), 7.58 (1H, d, $J=2.0\text{Hz}$), 7.87 (1H, s)
 FAB-MS(m/e): 392[M+H] $^+$

Manufacturing Example 19

[0229]

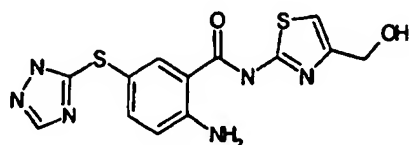


Preparation of 2-amino-5-(1-methyl-1H-tetrazol-5-ylsulfanyl)-N-(4-hydroxymethylthiazol-2-yl)benzamide

[0230] $^1\text{H NMR}(\text{CD}_3\text{OD})$ δ : 4.03 (3H, s), 4.60 (2H, s), 6.82 (1H, d, $J=8.8\text{Hz}$), 6.88 (1H, s), 7.43 (1H, dd, $J=2.4\text{Hz}$, 8.8Hz), 8.01 (1H, d, $J=2.4\text{Hz}$)
 FAB-MS(m/e): 364[M+H] $^+$

Manufacturing Example 20

[0231]

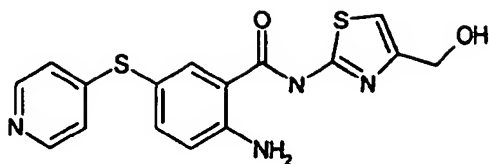


Preparation of 2-amino-5-(2H-[1,2,4]triazol-5-ylsulfanyl)-N-(4-hydroxymethylthiazol-2-yl)benzamide

[0232] $^1\text{H NMR}(\text{CD}_3\text{OD})$ δ : 4.60 (2H, s), 6.81 (1H, d, $J=8.8\text{Hz}$), 6.93 (1H, s), 7.42 (1H, dd, $J=2.0\text{Hz}$, 8.8Hz), 7.90 (1H, s), 8.01 (1H, d, $J=2.0\text{Hz}$), 8.27 (1H, brs)
 FAB-MS(m/e): 349[M+H] $^+$

Manufacturing Example 21

[0233]



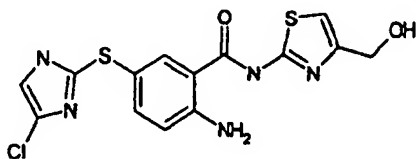
Preparation of 2-amino-5-(pyridine-4-ylsulfanyl)-N-(4-hydroxymethylthiazol-2-yl)benzamide

[0234] $^1\text{H NMR}(\text{CD}_3\text{OD})$ δ : 4.57 (1H, s), 6.91-6.94 (2H, m), 7.04 (2H, d, $J=4.8\text{Hz}$), 7.40 (1H, d, $J=8.8\text{Hz}$), 7.99 (1H, s), 8.23 (2H, d, $J=4.8\text{Hz}$)

FAB-MS(m/e): 359[M+H] $^+$

Manufacturing Example 22

[0235]



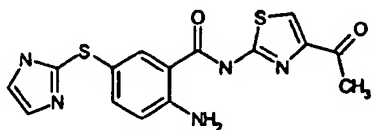
Preparation of 2-amino-5-(4-chloro-1H-imidazol-2-ylsulfanyl)-N-(4-hydroxymethylthiazol-2-yl)benzamide

[0236] $^1\text{H NMR}(\text{CD}_3\text{OD})$ δ : 4.60 (2H, s), 6.78 (1H, d, $J=8.4\text{Hz}$), 6.93 (1H, s), 7.05 (1H, s), 7.37 (1H, d, $J=8.4\text{Hz}$), 7.97 (1H, s)

FAB-MS(m/e): 382[M+H] $^+$

Manufacturing Example 23

[0237]



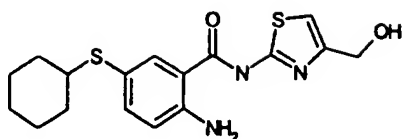
Preparation of 2-amino-5-(1H-imidazol-2-ylsulfanyl)-N-(4-acetylthiazol-2-yl)benzamide

[0238] $^1\text{H NMR}(\text{DMSO}-d_6)$ δ : 2.52 (3H, s), 6.74 (1H, d, $J=8.8\text{Hz}$), 6.90 (1H, s), 7.16 (1H, s), 7.24 (1H, d, $J=8.8\text{Hz}$), 8.13 (2H, s)

FAB-MS (m/e) : 360 [M+H] $^+$

Manufacturing Example 24

[0239]

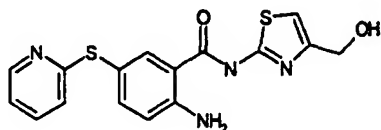


Preparation of 2-amino-5-cyclohexylsulfanyl-N-(4-hydroxymethylthiazol-2-yl)benzamide

[0240] $^1\text{H NMR}(\text{DMSO}-d_6)$ δ : 1.10-1.30 (6H, brs), 1.60-1.75 (2H, brs), 1.80-1.90 (2H, brs), 2.90-3.00 (1H, brs), 4.47 (2H, s), 5.20-5.22 (1H, brs), 6.71 (1H, dd, $J=2.8\text{Hz}$, 8.8Hz), 6.91 (1H, s), 7.24 (1H, d, $J=8.8\text{Hz}$), 7.93 (1H, s)
 FAB-MS(m/e): 364 $[\text{M}+\text{H}]^+$

Manufacturing Example 25

[0241]

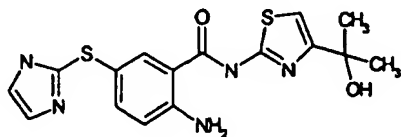


Preparation of 2-amino-5-(pyridin-2-ylsulfanyl)-N-(4-hydroxymethylthiazol-2-yl)benzamide

[0242] $^1\text{H NMR}(\text{CD}_3\text{OD})$ δ : 4.57 (2H, s), 6.80-6.92 (3H, m), 7.08 (1H, dt, $J=5.0\text{Hz}$, 7.6Hz), 7.42 (1H, dd, $J=1.6\text{Hz}$, 8.0Hz), 7.59 (1H, dt, $J=2.0\text{Hz}$, 7.6Hz), 8.01 (1H, d, $J=1.6\text{Hz}$), 8.31 (1H, d, $J=5.0\text{Hz}$)
 FAB-MS(m/e): 359 $[\text{M}+\text{H}]^+$

Manufacturing Example 26

[0243]

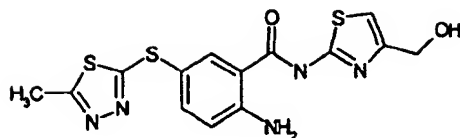


Preparation of 2-amino-5-(1H-imidazol-2-ylsulfanyl)-N-(4-(1-hydroxy-1-methylethyl)thiazol-2-yl)benzamide

[0244] $^1\text{H NMR}(\text{CD}_3\text{OD})$ δ : 1.56 (6H, s), 6.74 (1H, d, $J=8.8\text{Hz}$), 6.87 (1H, s), 7.05 (2H, s), 7.33 (1H, d, $J=8.8\text{Hz}$), 7.97 (1H, s)
 FAB-MS(m/e): 376 $[\text{M}+\text{H}]^+$

Manufacturing Example 27

[0245]

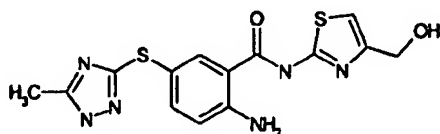


Preparation of 2-amino-5-(5-methyl-[1,3,4]thiadiazol-2-ylsulfanyl)-N-(4-hydroxymethylthiazol-2-yl)benzamide

[0246] $^1\text{H NMR}(\text{CDCl}_3)$ δ : 2.66 (3H, s), 4.63 (1H, s), 6.86 (1H, d, $J=8.4\text{Hz}$), 6.88 (1H, s), 7.51 (1H, dd, $J=2.0\text{Hz}$, 8.4Hz), 8.09 (1H, d, $J=2.0\text{Hz}$)
 FAB-MS(m/e): 380 $[\text{M}+\text{H}]^+$

Manufacturing Example 28

[0247]

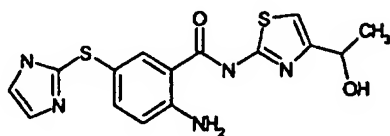


Preparation of 2-amino-5-(5-methyl-1H-[1,2,4]triazol-3-ylsulfanyl)-N-(4-hydroxymethylthiazol-2-yl)benzamide

[0248] $^1\text{H NMR}(\text{CD}_3\text{OD})$ δ : 2.36 (3H, s), 4.60 (2H, s), 6.79 (1H, d, $J=8.8\text{Hz}$), 6.93 (1H, s), 7.40 (1H, dd, $J=1.6\text{Hz}$, 8.8Hz), 7.98 (1H, d, $J=1.6\text{Hz}$)
 FAB-MS (m/e): 363 $[\text{M}+\text{H}]^+$

Manufacturing Example 29

[0249]

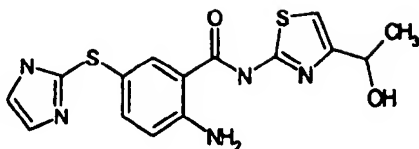


Preparation of 2-amino-5-(1H-imidazol-2-ylsulfanyl)-N-[4-(1-hydroxyethyl)thiazol-2-yl]benzamide

[0250] $^1\text{H NMR}(\text{CD}_3\text{OD})$ δ : 1.50 (3H, d, $J=6.8\text{Hz}$), 4.85 (1H, q, $J=6.8\text{Hz}$), 6.76 (1H, d, $J=8.8\text{Hz}$), 6.89 (1H, s), 7.05 (1H, s), 7.34 (1H, dd, $J=1.5\text{Hz}$, 8.8Hz), 7.96 (1H, d, $J=1.5\text{Hz}$)
 FAB-MS(m/e): 362 $[\text{M}+\text{H}]^+$

Manufacturing Example 30

[0251]



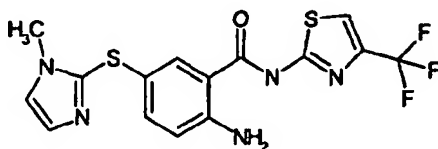
Preparation of 2-amino-5-(1H-imidazol-5-ylsulfanyl)-N-[4-(1-hydroxyethyl)thiazol-2-yl]benzamide

[0252] $^1\text{H NMR}(\text{CD}_3\text{OD})$ δ : 1.50 (3H, d, $J=6.8\text{Hz}$), 4.85 (1H, q, $J=6.8\text{Hz}$), 6.76 (1H, d, $J=8.8\text{Hz}$), 6.89 (1H, s), 7.05 (1H, s), 7.34 (1H, dd, $J=1.5\text{Hz}$, 8.8Hz), 7.96 (1H, d, $J=1.5\text{Hz}$)

FAB-MS(m/e): 362 $[\text{M}+\text{H}]^+$

Manufacturing Example 31

[0253]



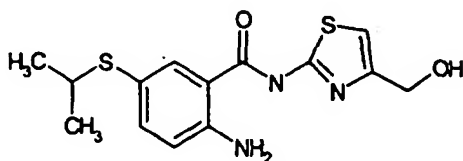
Preparation of 2-amino-5-(1-methyl-1H-imidazol-5-ylsulfanyl)-N-[4-(trifluoromethyl)thiazol-2-yl]benzamide

[0254] $^1\text{H NMR}(\text{CD}_3\text{OD})$ δ : 3.75 (3H, s), 6.75 (1H, d, $J=8.8\text{Hz}$), 7.02 (1H, s), 7.19 (1H, s), 7.29 (1H, dd, $J=1.2\text{Hz}$, 8.8Hz), 7.64 (1H, s), 7.95 (1H, d, $J=1.2\text{Hz}$)

FAB-MS(m/e): 400 $[\text{M}+\text{H}]^+$

Manufacturing Example 32

[0255]



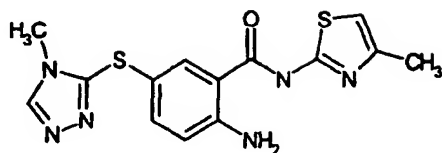
Preparation of 2-amino-5-(1-methylethyl)sulfanyl-N-[4-(hydroxymethyl)thiazol-2-yl]benzamide

[0256] $^1\text{H NMR}(\text{CD}_3\text{OD})$ δ : 1.21 (6H, d, $J=6.8\text{Hz}$), 3.14-3.18 (1H, m), 4.59 (2H, s), 6.76 (1H, d, $J=8.4\text{Hz}$), 6.93 (1H, s), 7.34 (1H, dd, $J=2.4\text{Hz}$, 8.4Hz), 7.83 (1H, d, $J=2.4\text{Hz}$)

FAB-MS(m/e): 324 $[\text{M}+\text{H}]^+$

Manufacturing Example 33

[0257]

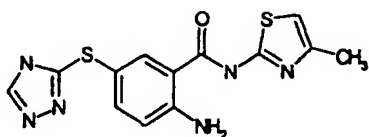


Preparation of 2-amino-5-(4-methyl-4H-[1,2,4]triazol-3-ylsulfanyl)-N-(4-methylthiazol-2-yl)benzamide

[0258] $^1\text{H NMR}(\text{CD}_3\text{OD})$ δ : 2.32 (3H, d, $J=1.0\text{Hz}$), 3.71 (3H, s), 6.62 (1H, d, $J=1.0\text{Hz}$), 6.78 (1H, d, $J=8.7\text{Hz}$), 7.36 (1H, dd, $J=2.2\text{Hz}$, 8.7Hz), 8.00 (1H, d, $J=2.2\text{Hz}$), 8.50 (1H, s)
 FAB-MS(m/e): 347 $[\text{M}+\text{H}]^+$

Manufacturing Example 34

[0259]

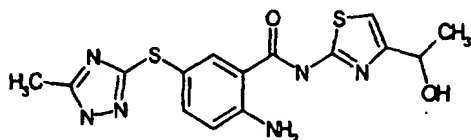


Preparation of 2-amino-5-(4H-[1,2,4]triazol-3-ylsulfanyl)-N-(4-methylthiazol-2-yl)benzamide

[0260] $^1\text{H NMR}(\text{CD}_3\text{OD})$ δ : 2.28 (3H, d, $J=1.0\text{Hz}$), 6.59 (1H, d, $J=1.0\text{Hz}$), 6.75 (1H, d, $J=8.6\text{Hz}$), 7.36 (1H, dd, $J=2.2\text{Hz}$, 8.6Hz), 7.97 (1H, d, $J=2.2\text{Hz}$), 8.22 (1H, s)
 FAB-MS(m/e): 333 $[\text{M}+\text{H}]^+$

Manufacturing Example 35

[0261]

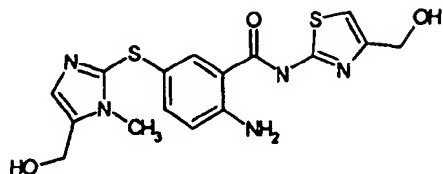


Preparation of 2-amino-5-(5-methyl-1H-[1,2,4]triazol-3-ylsulfanyl)-N-(4-(1-hydroxyethyl)thiazol-2-yl)benzamide

[0262] $^1\text{H NMR}(\text{CD}_3\text{OD})$ δ : 1.50 (3H, d, $J=6.6\text{Hz}$), 2.37 (3H, s), 4.84 (1H, q, $J=6.6\text{Hz}$), 6.79 (1H, d, $J=8.4\text{Hz}$), 6.89 (1H, s), 7.40 (1H, dd, $J=2.0\text{Hz}$, 8.4Hz), 7.99 (1H, d, $J=2.0\text{Hz}$)
 FAB-MS(m/e): 377 $[\text{M}+\text{H}]^+$

Manufacturing Example 36

[0263]

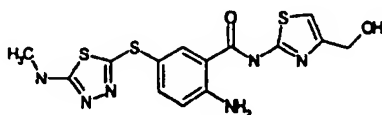


Preparation of 2-amino-5-(2-hydroxymethyl-1-methyl-1H-imidazol-3-ylsulfanyl)-N-(4-hydroxymethylthiazol-2-yl)benzamide

[0264] $^1\text{H NMR}(\text{CD}_3\text{OD})$ δ : 3.75 (3H, s), 4.55 (2H, s), 4.60 (2H, d, $J=0.8\text{Hz}$), 6.74 (1H, d, $J=8.7\text{Hz}$), 6.92 (1H, s), 6.99 (1H, s), 7.27 (1H, dd, $J=2.1\text{Hz}$, 8.7Hz), 7.90 (1H, d, $J=0.8\text{Hz}$)
 FAB-MS(m/e): 392[M+H] $^+$

Manufacturing Example 37

[0265]

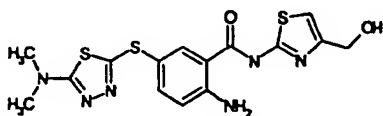


Preparation of 2-amino-5-(5-methylamino-[1,3,4]thiadiazol-2-ylsulfanyl)-N-(4-hydroxymethylthiazol-2-yl)benzamide

[0266] $^1\text{H NMR}(\text{CD}_3\text{OD})$ δ : 2.90 (3H, s), 4.59 (2H, s), 6.84 (1H, d, $J=8.8\text{Hz}$), 6.93 (1H, s), 7.46 (1H, dd, $J=2.0\text{Hz}$, 8.8Hz), 8.05 (1H, d, $J=2.0\text{Hz}$)
 FAB-MS(m/e): 395[M+H] $^+$

Manufacturing Example 38

[0267]

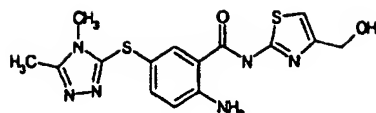


Preparation of 2-amino-5-(5-dimethylamino-[1,3,4]thiadiazol-2-ylsulfanyl)-N-(4-hydroxymethylthiazol-2-yl)benzamide

[0268] $^1\text{H NMR}(\text{CD}_3\text{OD})$ δ : 3.05 (6H, s), 4.59 (2H, s), 6.84 (1H, d, $J=8.8\text{Hz}$), 6.93 (1H, s), 7.46 (1H, dd, $J=2.0\text{Hz}$, 8.8Hz), 8.05 (1H, d, $J=2.0\text{Hz}$)
 FAB-MS(m/e): 409[M+H] $^+$

Manufacturing Example 39

[0269]

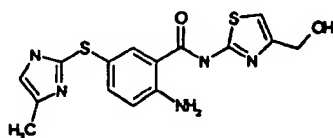


Preparation of 2-amino-5-(4,5-dimethyl-4H-[1,2,4]triazol-3-ylsulfanyl)-N-(4-hydroxymethylthiazol-2-yl)benzamide

[0270] $^1\text{H NMR}(\text{CD}_3\text{OD})$ δ : 2.42 (3H, s), 3.62 (3H, s), 4.60 (2H, s), 6.78 (1H, d, $J=8.8\text{Hz}$), 6.93 (1H, s), 7.37 (1H, dd, $J=2.1\text{Hz}$, 8.8Hz), 7.97 (1H, d, $J=2.1\text{Hz}$)
 FAB-MS(m/e): 377 $[\text{M}+\text{H}]^+$

Manufacturing Example 40

[0271]

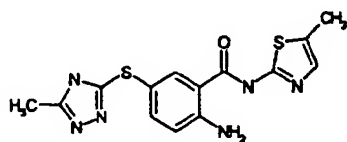


Preparation of 2-amino-5-(4-methyl-1H-imidazol-2-ylsulfanyl)-N-(4-hydroxymethylthiazol-2-yl)benzamide

[0272] $^1\text{H NMR}(\text{CD}_3\text{OD})$ δ : 2.00 (3H, s), 4.60 (2H, s), 6.74 (1H, s), 6.75 (1H, d, $J=8.4\text{Hz}$), 6.93 (1H, s), 7.32 (1H, dd, $J=2.0\text{Hz}$, 8.4Hz), 7.93 (1H, d, $J=2.0\text{Hz}$)
 FAB-MS(m/e): 362 $[\text{M}+\text{H}]^+$

Manufacturing Example 41

[0273]



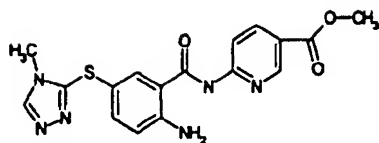
Preparation of 2-amino-5-(5-methyl-4H-[1,2,4]triazol-3-ylsulfanyl)-N-(5-methylthiazol-2-yl)benzamide

[0274] $^1\text{H NMR}(\text{CD}_3\text{OD})$ δ : 2.35 (3H, s), 2.38 (3H, d, $J=1.1\text{Hz}$), 6.77 (1H, d, $J=8.6\text{Hz}$), 7.09 (1H, d, $J=1.1\text{Hz}$), 7.38 (1H, dd, $J=2.0\text{Hz}$, 8.6Hz), 7.97 (1H, d, $J=2.0\text{Hz}$)
 FAB-MS(m/e): 347 $[\text{M}+\text{H}]^+$

Manufacturing Example 42

[0275]

5



10

Preparation of 2-amino-5-(4-methyl-4H-[1,2,4]triazol-3-ylsulfanyl)-N-(5-ethoxycarbonylpyridin-2-yl)benzamide

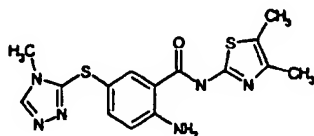
[0276] $^1\text{H NMR}(\text{CD}_3\text{OD})$ δ : 3.72 (3H, s), 3.92 (3H, s), 6.79 (1H, d, $J=8.7\text{Hz}$), 7.38 (1H, dd, $J=2.1\text{Hz}$, 8.7Hz), 7.96 (1H, d, $J=2.1\text{Hz}$), 8.30-8.32 (2H, m), 8.51 (1H, s), 8.91-8.93 (1H, s)
FAB-MS(m/e): 385 $[\text{M}+\text{H}]^+$

15

Manufacturing Example 43

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[0277]



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Preparation of 2-amino-5-(4-methyl-4H-[1,2,4]triazol-3-ylsulfanyl)-N-(4,5-dimethylthiazol-2-yl)benzamide

30

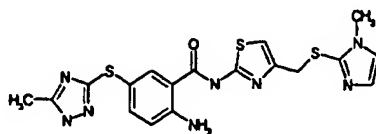
[0278] $^1\text{H NMR}(\text{CD}_3\text{OD})$ δ : 2.17 (3H, s), 2.22 (3H, s), 3.58 (3H, s), 6.75 (1H, d, $J=8.6\text{Hz}$), 7.26 (1H, dd, $J=2.2\text{Hz}$, 8.6Hz), 8.09 (1H, d, $J=2.2\text{Hz}$), 8.57 (1H, s)
FAB-MS(m/e): 361 $[\text{M}+\text{H}]^+$

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Manufacturing Example 44

[0279]

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Preparation of 2-amino-5-(5-methyl-4H-[1,2,4]triazol-3-ylsulfanyl)-N-[4-(1-methyl-1H-imidazol-2-ylsulfanylmethyl)thiazol-2-yl]benzamide

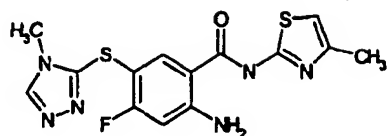
[0280] $^1\text{H NMR}(\text{CD}_3\text{OD})$ δ : 2.38 (3H, s), 3.47 (3H, s), 4.10 (2H, s), 6.54 (1H, s), 6.78 (1H, d, $J=8.8\text{Hz}$), 7.04 (1H, d, $J=1.2\text{Hz}$), 7.13 (1H, d, $J=1.2\text{Hz}$), 7.40 (1H, dd, $J=2.0\text{Hz}$, 8.8Hz), 7.98 (1H, d, $J=2.0\text{Hz}$)
FAB-MS(m/e): 459 $[\text{M}+\text{H}]^+$

50

55

Manufacturing Example 45

[0281]



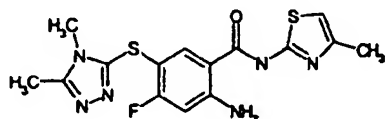
Preparation of 2-amino-4-fluoro-5-(4-methyl-4H-[1,2,4]triazol-3-ylsulfanyl)-N-(4-methylthiazol-2-yl)benzamide

[0282] $^1\text{H NMR}(\text{CD}_3\text{OD})$ δ : 2.32 (3H, s), 3.77 (3H, s), 6.56 (1H, d, $J=11.6\text{Hz}$), 6.62 (1H, s), 8.13 (1H, d, $J=8.0\text{Hz}$), 8.51 (1H, s)

FAB-MS(m/e): 365 $[\text{M}+\text{H}]^+$

Manufacturing Example 46

[0283]



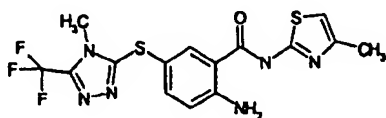
Preparation of 2-amino-4-fluoro-5-(4,5-dimethyl-4H-[1,2,4]triazol-3-ylsulfanyl)-N-(4-methylthiazol-2-yl)benzamide

[0284] $^1\text{H NMR}(\text{CD}_3\text{OD})$ δ : 2.33 (3H, s), 2.43 (3H, s), 3.67 (3H, s), 6.54 (1H, d, $J=11.6\text{Hz}$), 6.62 (1H, s), 8.11 (1H, d, $J=7.6\text{Hz}$)

FAB-MS(m/e): 379 $[\text{M}+\text{H}]^+$

Manufacturing Example 47

[0285]



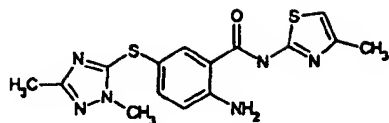
Preparation of 2-amino-5-(4-methyl-5-trifluoromethyl-4H-[1,2,4]triazol-3-ylsulfanyl)-N-(4-methylthiazol-2-yl)benzamide

[0286] $^1\text{H NMR}(\text{CDCl}_3)$ δ : 2.16 (3H, s), 3.68 (3H, s), 6.47 (1H, s), 6.63 (1H, d, $J=9.2\text{Hz}$), 7.35 (1H, dd, $J=1.2\text{Hz}$, $J=9.2\text{Hz}$), 7.87 (1H, d, $J=1.2\text{Hz}$)

FAB-MS(m/e): 415 $[\text{M}+\text{H}]^+$

Manufacturing Example 48

[0287]



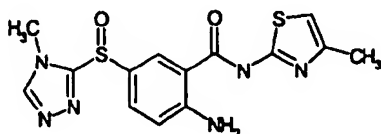
Preparation of 2-amino-5-(2,5-dimethyl-2H-[1,2,4]triazol-3-ylsulfanyl)-N-(4-methylthiazol-2-yl)benzamide

[0288] $^1\text{H NMR}(\text{CD}_3\text{OD})$ δ : 2.25 (3H, s), 2.33 (3H, s), 3.84 (3H, s), 6.64 (1H, s), 6.79 (1H, d, $J=8.8\text{Hz}$), 7.37 (1H, dd, $J=2.0\text{Hz}$, 8.8Hz), 8.00 (1H, d, $J=2.0\text{Hz}$)

FAB-MS(m/e): 361 $[\text{M}+\text{H}]^+$

Manufacturing Example 49

[0289]



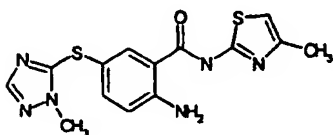
Preparation of 2-amino-5-(4-methyl-4H-[1,2,4]triazol-3-ylsulfinyl)-N-(4-methylthiazol-2-yl)benzamide

[0290] $^1\text{H NMR}(\text{CD}_3\text{OD})$ δ : 2.32 (3H, d, $J=0.8\text{Hz}$), 3.81 (3H, s), 6.62 (1H, s), 6.95 (1H, d, $J=8.9\text{Hz}$), 7.54 (1H, dd, $J=2.2\text{Hz}$, 8.9Hz), 8.26 (1H, d, $J=2.2\text{Hz}$), 8.57 (1H, s)

FAB-MS(m/e): 363 $[\text{M}+\text{H}]^+$

Manufacturing Example 50

[0291]



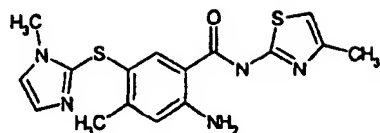
Preparation of 2-amino-5-(2-methyl-2H-[1,2,4]triazol-3-ylsulfanyl)-N-(4-methylthiazol-2-yl)benzamide

[0292] $^1\text{H NMR}(\text{CDCl}_3)$ δ : 2.21 (3H, s), 3.84 (3H, s), 6.01 (2H, br), 6.69 (1H, d, $J=8.4\text{Hz}$), 7.43 (1H, d, $J=8.4\text{Hz}$), 7.78 (1H, s), 7.83 (1H, s)

FAB-MS(m/e): 347 $[\text{M}+\text{H}]^+$

Manufacturing Example 51

[0293]



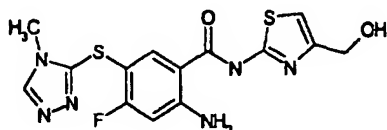
Preparation of 2-amino-4-methyl-5-(1-methyl-1H-imidazol-2-ylsulfanyl)-N-(4-methylthiazol-2-yl)benzamide

[0294] $^1\text{H NMR}(\text{CDCl}_3)$ δ : 2.35 (3H, s), 2.38 (3H, s), 3.71 (3H, s), 6.51 (1H, s), 6.56 (1H, s), 6.94 (1H, s), 7.03 (1H, s), 7.93 (1H, s)

FAB-MS(m/e): 360[M+H] $^+$

Manufacturing Example 52

[0295]



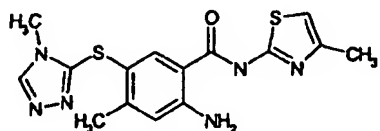
Preparation of 2-amino-4-fluoro-5-(4-methyl-4H-[1,2,4]triazol-3-ylsulfanyl)-N-(4-hydroxymethylthiazol-2-yl)benzamide

[0296] $^1\text{H NMR}(\text{CD}_3\text{OD})$ δ : 3.78 (3H, s), 4.60 (2H, s), 6.58 (1H, d, $J_{\text{H-F}}=11.4\text{Hz}$), 6.93 (1H, s), 8.12 (1H, d, $J_{\text{H-F}}=7.7\text{Hz}$), 8.52 (1H, s)

FAB-MS(m/e): 381[M+H] $^+$

Manufacturing Example 53

[0297]



Preparation of 2-amino-4-methyl-5-(4-methyl-4H-[1,2,4]triazol-3-ylsulfanyl)-N-(4-methylthiazol-2-yl)benzamide

[0298] $^1\text{H NMR}(\text{CD}_3\text{OD})$ δ : 2.32 (3H, s), 2.34 (3H, s), 3.71 (3H, s), 6.63 (1H, s), 6.73 (1H, s), 8.02 (1H, s), 8.48 (1H, s)

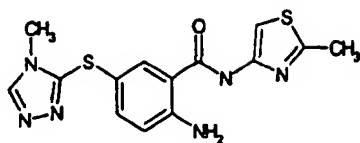
FAB-MS(m/e): 361[M+H] $^+$

Manufacturing Example 54

[0299]

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Preparation of 2-amino-5-(4-methyl-4H-(1,2,4)triazol-3-ylsulfanyl)-N-(2-methylthiazol-4-yl)benzamide

15

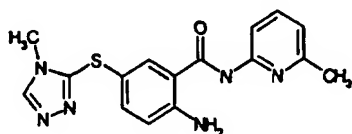
[0300] $^1\text{H NMR}$ (CD_3OD) δ : 2.65 (3H, s), 3.72 (3H, s), 6.77 (1H, d, $J=8.8\text{Hz}$), 7.36 (1H, dd, $J=2.0\text{Hz}$, 8.8Hz), 7.51 (1H, s), 7.89 (1H, d, $J=2.0\text{Hz}$), 8.52 (1H, s)
 FAB-MS(m/e): 347 $[\text{M}+\text{H}]^+$

Manufacturing Example 55

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[0301]

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Preparation of 2-amino-5-(4-methyl-4H-[1,2,4]triazol-3-ylsulfanyl)-N-(6-methylpyridin-2-yl)benzamide

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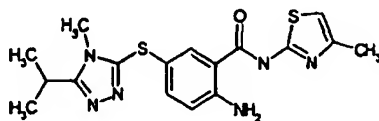
[0302] $^1\text{H NMR}$ (CD_3OD) δ : 2.47 (3H, s), 3.73 (3H, s), 6.78 (1H, d, $J=8.7\text{Hz}$), 7.01 (1H, d, $J=7.7\text{Hz}$), 7.36 (1H, dd, $J=2.2\text{Hz}$, 8.7Hz), 7.69 (1H, t, $J=7.7\text{Hz}$), 7.94 (1H, d, $J=2.2\text{Hz}$), 7.96 (1H, d, $J=7.7\text{Hz}$), 8.51 (1H, s)
 FAB-MS(m/e): 341 $[\text{M}+\text{H}]^+$

Manufacturing Example 56

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[0303]

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Preparation of 2-amino-5-(5-isopropyl-4-methyl-4H-[1,2,4]triazol-3-ylsulfanyl)-N-(4-methylthiazol-2-yl)benzamide

50

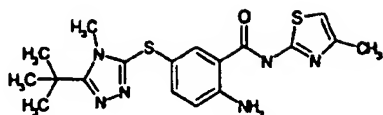
[0304] $^1\text{H NMR}$ (CD_3OD) δ : 1.32 (6H, d, $J=6.9\text{Hz}$), 2.32 (3H, s), 3.09-3.13 (1H, m), 3.65 (3H, s), 6.63 (1H, s), 6.77 (1H, d, $J=8.7\text{Hz}$), 7.35 (1H, dd, $J=2.2\text{Hz}$, 8.7Hz), 7.99 (1H, d, $J=2.2\text{Hz}$)
 FAB-MS(m/e): 389 $[\text{M}+\text{H}]^+$

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Manufacturing Example 57

[0305]

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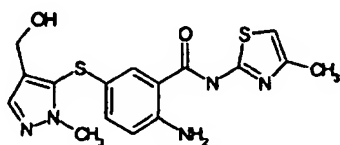
Preparation of 2-amino-4-fluoro-5-(5-tert-butyl-4-methyl-4H-[1,2,4]triazol-3-ylsulfanyl)-N-(4-methylthiazol-2-yl)benzamide

15 **[0306]** $^1\text{H NMR}(\text{CD}_3\text{OD})$ δ : 1.43 (9H, s), 2.33 (3H, d, $J=1.0\text{Hz}$), 3.83 (3H, s), 6.63 (1H, s), 6.78 (1H, d, $J=8.7\text{Hz}$), 7.35 (1H, dd, $J=2.2\text{Hz}$, 8.7Hz), 8.00 (1H, d, $J=2.2\text{Hz}$)
FAB-MS(m/e): 403 $[\text{M}+\text{H}]^+$

Manufacturing Example 58

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[0307]



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Preparation of 2-amino-5-(5-hydroxymethyl-2-methyl-2H-pyrazol-3-ylsulfanyl)-N-(4-methylthiazol-2-yl)benzamide

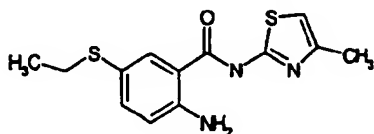
30 **[0308]** $^1\text{H NMR}(\text{CD}_3\text{OD})$ δ : 2.32 (3H, s), 3.86 (3H, s), 4.61 (2H, s), 6.63 (1H, s), 6.73 (1H, d, $J=8.8\text{Hz}$), 7.18 (1H, d, $J=2.0\text{Hz}$, 8.8Hz), 7.58 (1H, s), 7.81 (1H, d, $J=2.0\text{Hz}$)
FAB-MS(m/e): 376 $[\text{M}+\text{H}]^+$

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Manufacturing Example 59

[0309]

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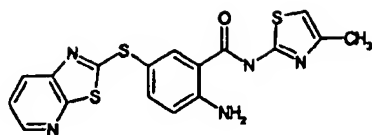
Preparation of 2-amino-5-ethylsulfanyl-N-(4-methylthiazol-2-yl)benzamide

50 **[0310]** $^1\text{H NMR}(\text{CDCl}_3)$ δ : 1.18 (3H, t, $J=7.2\text{Hz}$), 2.20 (3H, s), 2.69 (2H, q, $J=7.2\text{Hz}$), 6.53 (1H, s), 6.67 (1H, d, $J=8.8\text{Hz}$), 7.34 (1H, dd, $J=2.4\text{Hz}$, 8.8Hz), 7.61 (1H, d, $J=2.4\text{Hz}$)
FAB-MS(m/e): 294 $[\text{M}+\text{H}]^+$

55

Manufacturing Example 60

[0311]

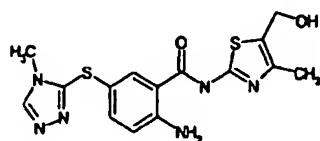


Preparation of 2-amino-5-(thiazolo[5,4-b]pyridin-2-ylsulfanyl)-N-(4-methylthiazol-2-yl)benzamide

[0312] $^1\text{H NMR}(\text{CD}_3\text{OD})$ δ : 2.28 (3H, s), 6.61 (1H, s), 6.93 (1H, d, $J=8.8\text{Hz}$), 7.44 (1H, dd, $J=4.8\text{Hz}$, 8.4Hz), 7.53 (1H, dd, $J=2.4\text{Hz}$, 8.8Hz), 8.07 (1H, dd, $J=1.6\text{Hz}$, 8.4Hz), 8.19 (1H, d, $J=2.4\text{Hz}$), 8.37 (1H, dd, $J=1.6\text{Hz}$, 4.8Hz)
 FAB-MS(m/e): 400 $[\text{M}+\text{H}]^+$

Manufacturing Example 61

[0313]

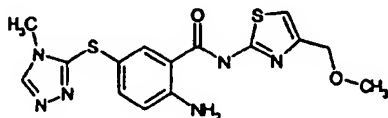


Preparation of 2-amino-5-(4-methyl-4H-[1,2,4]triazol-3-ylsulfanyl)-N-(5-hydroxymethyl-4-methylthiazol-2-yl)benzamide

[0314] $^1\text{H NMR}(\text{CD}_3\text{OD})$ δ : 2.29 (3H, s), 3.71 (3H, s), 4.66 (2H, s), 6.78 (1H, d, $J=8.8\text{Hz}$), 7.36 (1H, dd, $J=1.9\text{Hz}$, 8.8Hz), 8.00 (1H, d, $J=1.9\text{Hz}$), 8.50 (1H, s)
 FAB-MS(m/e): 377 $[\text{M}+\text{H}]^+$

Manufacturing Example 62

[0315]



Preparation of 2-amino-5-(4-methyl-4H-[1,2,4]triazol-3-ylsulfanyl)-N-(4-methoxymethylthiazol-2-yl)benzamide

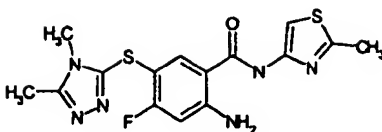
[0316] $^1\text{H NMR}(\text{CD}_3\text{OD})$ δ : 3.40 (3H, s), 3.72 (3H, s), 4.46 (2H, s), 6.80 (1H, d, $J=8.8\text{Hz}$), 7.00 (1H, s), 7.39 (1H, dd, $J=2.0\text{Hz}$, 8.8Hz), 7.99 (1H, d, $J=2.0\text{Hz}$), 8.51 (1H, s)
 FAB-MS(m/e): 377 $[\text{M}+\text{H}]^+$

Manufacturing Example 63

[0317]

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Preparation of 2-amino-5-(4,5-dimethyl-4H-[1,2,4]triazol-3-ylsulfanyl)-N-(2-methylthiazol-4-yl)benzamide

15

[0318] $^1\text{H NMR}(\text{CD}_3\text{OD})$ δ : 2.42 (3H, s), 2.65 (3H, s), 3.67 (3H, s), 6.53 (1H, d, $J=11.2\text{Hz}$), 7.49 (1H, s), 7.99 (1H, d, $J=7.6\text{Hz}$)

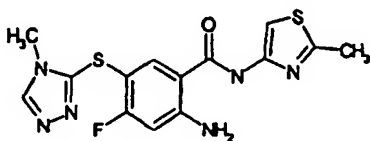
FAB-MS(m/e): 379[$\text{M}+\text{H}$] $^+$

Manufacturing Example 64

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[0319]

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Preparation of 2-amino-4-fluoro-5-(4-methyl-4H-[1,2,4]triazol-3-ylsulfanyl)-N-(2-methylthiazol-4-yl)benzamide

[0320] $^1\text{H NMR}(\text{CD}_3\text{OD})$ δ : 2.65 (3H, s), 3.77 (3H, s), 6.54 (1H, d, $J=11.2\text{Hz}$), 7.49 (1H, s), 8.00 (1H, d, $J=8.0\text{Hz}$), 8.49 (1H, s)

35

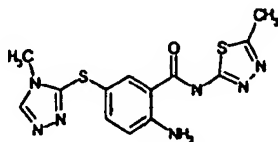
FAB-MS(m/e): 365[$\text{M}+\text{H}$] $^+$

Manufacturing Example 65

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[0321]

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Preparation of 2-amino-5-(4-methyl-4H-[1,2,4]triazol-3-ylsulfanyl)-N-(5-methyl-[1,3,4]thiadiazol-2-yl)benzamide

50

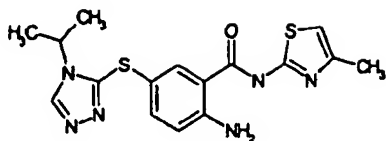
[0322] $^1\text{H NMR}(\text{CD}_3\text{OD})$ δ : 2.68 (3H, s), 3.71 (3H, s), 6.80 (1H, d, $J=8.4\text{Hz}$), 7.39 (1H, dd, $J=2.0\text{Hz}$, 8.4Hz), 8.06 (1H, d, $J=2.0\text{Hz}$), 8.51 (1H, s)

FAB-MS(m/e): 348[$\text{M}+\text{H}$] $^+$

55

Manufacturing Example 66

[0323]



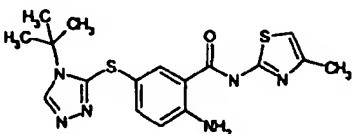
Preparation of 2-amino-5-(4-isopropyl-4H-[1,2,4]triazol-3-ylsulfanyl)-N-(4-methylthiazol-2-yl)benzamide

[0324] $^1\text{H NMR}$ (CDCl_3) δ : 1.47 (6H, d, $J=6.8\text{Hz}$), 2.33 (3H, s), 4.62 (1H, sep, $J=6.8\text{Hz}$), 6.00 (2H, br), 6.55 (1H, s), 6.69 (1H, d, $J=8.4\text{Hz}$), 7.44 (1H, dd, $J=1.6\text{Hz}$, 8.4Hz), 7.96 (1H, d, $J=1.6\text{Hz}$), 8.26 (1H, s)

FAB-MS(m/e): 375 $[\text{M}+\text{H}]^+$

Manufacturing Example 67

[0325]



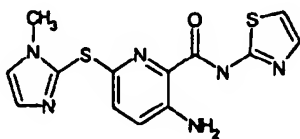
Preparation of 2-amino-5-(4-tert-butyl-4H-[1,2,4]triazol-3-ylsulfanyl)-N-(4-methylthiazol-2-yl)benzamide

[0326] $^1\text{H NMR}$ (CDCl_3) δ : 1.74 (9H, s), 2.32 (3H, s), 5.98 (2H, br), 6.53 (1H, s), 6.70 (1H, d, $J=8.8\text{Hz}$), 7.48 (1H, d, $J=8.8\text{Hz}$), 7.94 (1H, s), 8.22 (1H, s)

FAB-MS(m/e): 389 $[\text{M}+\text{H}]^+$

Manufacturing Example 68

[0327]



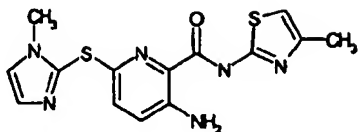
Preparation of 3-amino-6-(1-methyl-1H-imidazol-2-ylsulfanyl)pyridine-2-carboxylic acid thiazol-2-ylamide

[0328] $^1\text{H NMR}$ (CDCl_3) δ : 3.75 (3H, s), 5.94 (2H, br.s), 6.95-7.05 (3H, m), 7.21 (1H, br.s), 7.28 (1H, br.s), 7.51 (1H, d, $J=3.9\text{Hz}$)

FAB-MS(m/e): 333 $[\text{M}+\text{H}]^+$

Manufacturing Example 69

[0329]



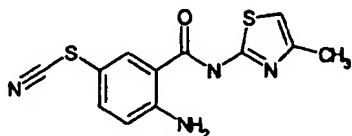
Preparation of 3-amino-6-(1-methyl-1H-imidazol-2-ylsulfanyl)pyridine-2-carboxylic acid 4-methylthiazol-2-ylamide

[0330] $^1\text{H NMR}(\text{CDCl}_3)$ δ : 2.39 (3H, s), 3.73 (3H, s), 5.93 (2H, br.s), 6.56 (1H, s), 6.91-7.00 (2H, m), 7.16 (1H, br.s), 7.24 (1H, br.s)

FAB-MS(m/e): 347[M+H]⁺

Manufacturing Example 70

[0331]



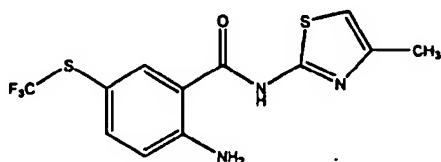
Preparation of 2-amino-5-thiocyanato-N-(4-methylthiazol-2-yl)benzamide

[0332] $^1\text{H NMR}(\text{CD}_3\text{OD})$ δ : 2.32 (3H, s), 6.63 (1H, s), 6.87 (1H, d, J=8.8Hz), 7.47 (1H, dd, J=2.0Hz, 8.8Hz), 8.08 (1H, d, J=2.0Hz)

FAB-MS(m/e): 291[M+H]⁺

Manufacturing Example 71

[0333]



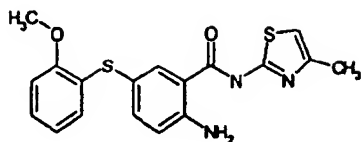
Preparation of 2-amino-5-(trifluoromethylsulfanyl)-N-(4-methylthiazol-2-yl)benzamide

[0334] $^1\text{H NMR}(\text{CDCl}_3)$ δ : 2.06 (3H, s), 6.58 (1H, s), 7.54 (1H, t, J=8.0Hz), 7.86 (1H, d, J=8.0Hz), 7.99 (1H, d, J=8.0Hz), 8.20 (1H, s)

FAB-MS(m/e): 319[M+H]⁺

Manufacturing Example 72

[0335]

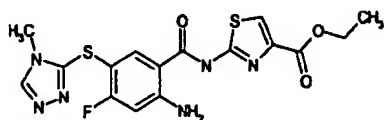


Preparation of 2-amino-5-(2-methoxyphenylsulfanyl)-N-(4-methylthiazol-2-yl)benzamide

[0336] $^1\text{H NMR}(\text{CDCl}_3)$ δ : 2.26-2.33 (3H, m), 3.90 (3H, s), 5.94 (1H, br), 6.52 (1H, d, $J=1.0\text{Hz}$), 6.72-6.86 (4H, m), 7.09-7.15 (1H, m), 7.41 (1H, dd, $J=2.0\text{Hz}$, 8.5Hz), 7.69 (1H, s)
 FAB-MS(m/e): 372 $[\text{M}+\text{H}]^+$

Manufacturing Example 73

[0337]

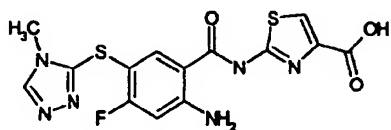


Preparation of 2-amino-4-fluoro-5-(4-methyl-4H-[1,2,4]triazol-3-ylsulfanyl)-N-(4-ethoxycarbonylthiazol-2-yl)benzamide

[0338] $^1\text{H NMR}(\text{DMSO}-d_6)$ δ : 1.31 (3H, t, $J=7.0\text{Hz}$), 3.64 (3H, s), 4.29 (2H, q, $J=7.0\text{Hz}$), 6.65 (1H, d, $J_{\text{H-F}}=11.6\text{Hz}$), 7.29 (2H, brs), 8.09 (1H, s), 8.34 (1H, s), 8.57 (1H, s)
 FAB-MS(m/e): 423 $[\text{M}+\text{H}]^+$

Manufacturing Example 74

[0339]

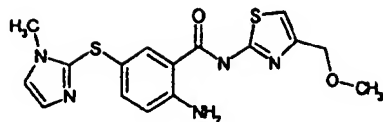


Preparation of 2-amino-4-fluoro-5-(4-methyl-4H-[1,2,4]triazol-3-ylsulfanyl)-N-(4-carboxylthiazol-2-yl)benzamide

[0340] $^1\text{H NMR}(\text{CDCl}_3)$ δ : 3.81 (3H, s), 6.62 (1H, d, $J_{\text{H-F}}=11.0\text{Hz}$), 8.00 (1H, s), 8.21 (1H, d, $J_{\text{H-F}}=4.8\text{Hz}$), 8.57 (1H, s)
 FAB-MS(m/e): 395 $[\text{M}+\text{H}]^+$

Manufacturing Example 75

[0341]

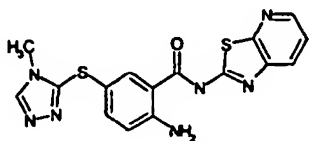


Preparation of 2-amino-5-(1-methyl-1H-imidazol-2-ylsulfanyl)-N-(4-methylthiazol-2-yl)benzamide

[0342] $^1\text{H NMR}(\text{CDCl}_3)$ δ : 3.45 (3H, s), 3.70 (3H, s), 4.47 (2H, s), 5.82-5.86 (2H, brs), 6.64 (1H, d, $J=8.8\text{Hz}$), 6.87 (1H, s), 6.96 (1H, s), 7.06 (1H, s), 7.37 (1H, dd, $J=1.6\text{Hz}$, 8.8Hz), 7.88 (1H, d, $J=1.6\text{Hz}$)
 FAB-MS(m/e): 376 $[\text{M}+\text{H}]^+$

Manufacturing Example 76

[0343]

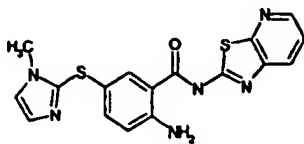


Preparation of 2-amino-5-(4-methyl-4H-[1,2,4]triazol-3-ylsulfanyl)-N-thiazolo[5,4-b]pyridin-2-ylbenzamide

[0344] $^1\text{H NMR}(\text{DMSO}-d_6)$ δ : 3.59 (3H, s), 6.80 (1H, d, $J=8.8\text{Hz}$), 7.30 (1H, d, $J=8.8\text{Hz}$), 7.47 (1H, br), 8.07 (1H, br), 8.16 (1H, s), 8.44 (1H, d, $J=4.8\text{Hz}$), 8.57 (1H, s)
 FAB-MS(m/e): 384 $[\text{M}+\text{H}]^+$

Manufacturing Example 77

[0345]

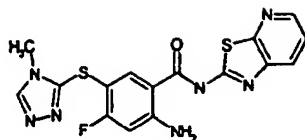


Preparation of 2-amino-5-(1-methyl-1H-imidazol-2-ylsulfanyl)-N-thiazolo[5,4-b]pyridin-2-ylbenzamide

[0346] $^1\text{H NMR}(\text{CD}_3\text{OD})$ δ : 6.79 (1H, d, $J=8.8\text{Hz}$), 7.07 (1H, br), 7.24 (1H, br), 7.32 (1H, dd, $J=2.0\text{Hz}$, 8.8Hz), 7.49 (1H, dt, $J=4.8\text{Hz}$, 8.0Hz), 8.02 (1H, d, $J=2.0\text{Hz}$), 8.10 (1H, d, $J=8.0\text{Hz}$), 8.43 (1H, d, $J=4.8\text{Hz}$)
 FAB-MS(m/e): 383 $[\text{M}+\text{H}]^+$

Manufacturing Example 78

[0347]



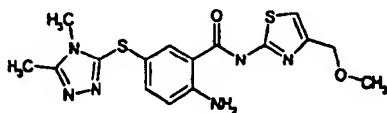
Preparation of 2-amino-4-fluoro-5-(4-methyl-4H-[1,2,4]triazol-3-ylsulfanyl)-N-thiazolo[5,4-b]pyridin-2-ylbenzamide

[0348] $^1\text{H NMR}(\text{DMSO}-d_6)$ δ : 3.62 (3H, s), 6.64 (1H, d, $J=12.0\text{Hz}$), 7.47 (1H, br), 8.05 (1H, br), 8.33 (1H, d, $J=8.7\text{Hz}$), 8.44 (1H, br), 8.55 (1H, s)

FAB-MS(m/e): 402[M+H] $^+$

Manufacturing Example 79

[0349]



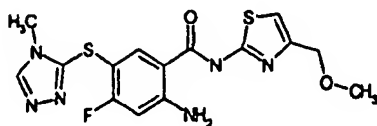
Preparation of 2-amino-5-(4,5-dimethyl-4H-[1,2,4]triazol-3-ylsulfanyl)-N-(4-methoxymethylthiazol-2-yl)benzamide

[0350] $^1\text{H NMR}(\text{CD}_3\text{OD})$ δ : 2.41 (3H, s), 3.39 (3H, s), 3.61 (3H, s), 4.45 (2H, s), 6.77 (1H, d, $J=8.8\text{Hz}$), 6.98 (1H, s), 7.36 (1H, dd, $J=2.4\text{Hz}$, 8.8Hz), 7.97 (1H, d, $J=2.4\text{Hz}$)

FAB-MS(m/e): 391[M+H] $^+$

Manufacturing Example 80

[0351]



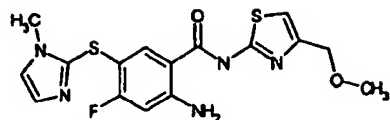
Preparation of 2-amino-4-fluoro-5-(4,5-dimethyl-4H-[1,2,4]triazol-3-ylsulfanyl)-N-(4-methoxymethylthiazol-2-yl)benzamide

[0352] $^1\text{H NMR}(\text{DMSO}-d_6)$ δ : 3.14 (3H, s), 3.60 (3H, s), 4.38 (2H, s), 6.61 (1H, d, $J=12\text{Hz}$), 7.06 (1H, s), 7.18-7.30 (2H, brs), 8.24 (1H, d, $J=8.0\text{Hz}$), 8.54 (1H, s)

FAB-MS(m/e): 395[M+H] $^+$

Manufacturing Example 81

[0353]



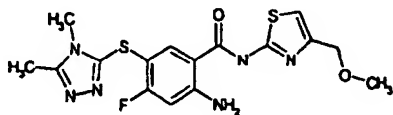
Preparation of 2-amino-4-fluoro-5-(1-methyl-1H-imidazol-2-ylsulfanyl)-N-(4-methoxymethylthiazol-2-yl)benzamide

[0354] $^1\text{H NMR}(\text{CDCl}_3)$ δ : 3.42 (3H, s), 3.76 (3H, s), 4.44 (2H, s), 6.08-6.18 (2H, brs), 6.35 (1H, d, $J=10.4\text{Hz}$), 6.84 (1H, s), 6.93 (1H, s), 7.02 (1H, s), 8.05 (1H, d, $J=7.6\text{Hz}$)

FAB-MS(m/e): 394 $[\text{M}+\text{H}]^+$

Manufacturing Example 82

[0355]



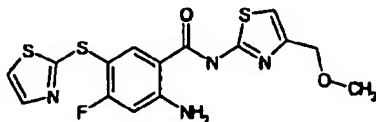
Preparation of 2-amino-4-fluoro-5-(4,5-dimethyl-4H-[1,2,4]triazol-3-ylsulfanyl)-N-(4-methoxymethylthiazol-2-yl)benzamide

[0356] $^1\text{H NMR}(\text{CDCl}_3)$ δ : 2.40 (3H, s), 3.40 (3H, s), 3.59 (3H, s), 4.41 (2H, s), 6.20-6.28 (2H, brs), 6.30 (1H, d, $J=10.8\text{Hz}$), 6.80 (1H, s), 8.10 (1H, d, $J=7.6\text{Hz}$)

FAB-MS(m/e): 409 $[\text{M}+\text{H}]^+$

Manufacturing Example 83

[0357]



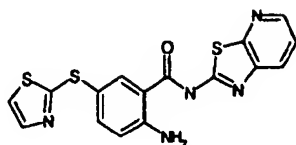
Preparation of 2-amino-5-(thiazol-2-ylsulfanyl)-N-(4-methoxymethylthiazol-2-yl)benzamide

[0358] $^1\text{H NMR}(\text{CDCl}_3)$ δ : 3.43 (3H, s), 4.45 (2H, s), 6.24-6.30 (2H, brs), 6.51 (1H, d, $J=10.8\text{Hz}$), 6.88 (1H, s), 7.19 (1H, d, $J=2.0\text{Hz}$), 7.65 (1H, d, $J=2.0\text{Hz}$), 7.92 (1H, d, $J=6.8\text{Hz}$)

FAB-MS(m/e): 397 $[\text{M}+\text{H}]^+$

Manufacturing Example 84

[0359]

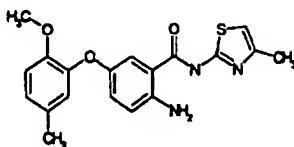


Preparation of 2-amino-5-(thiazol-2-ylsulfanyl)-N-thiazolo[5,4-b]pyridin-2-ylbenzamide

[0360] $^1\text{H NMR}(\text{CD}_3\text{OD})$ δ : 6.92 (1H, d, $J=8.4\text{Hz}$), 7.40 (1H, d, $J=3.6\text{Hz}$), 7.45-7.49 (1H, m), 7.53 (1H, d, $J=8.4\text{Hz}$), 7.63 (1H, d, $J=3.6\text{Hz}$), 8.08 (1H, d, $J=8.0\text{Hz}$), 8.22 (1H, s), 8.43 (1H, d, $J=4.8\text{Hz}$)
 FAB-MS(m/e): 386[$\text{M}+\text{H}$] $^+$

Manufacturing Example 85

[0361]



Preparation of 2-amino-5-(2-methoxy-5-methylphenoxy)-N-(4-methoxymethylthiazol-2-yl)benzamide

[0362] Three drops of N,N -dimethylformamide and 4.07 ml (46.6 mmol) of oxalyl chloride were dripped into a methylene chloride solution (100 ml) of 7.84 g (42.4 mmol) of 5-fluoro-2-nitrobenzoic acid on ice, and after the addition was completed, the reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure, and an acid chloride was obtained as a colorless oily material.

[0363] 7.00 ml (50.8 mmol) of triethylamine was added to a methylene chloride solution (50 ml) of 5.80 g (50.8 mmol) of 2-aminothiazole, the methylene chloride solution (30 ml) of the acid chloride previously obtained was dripped in on ice, and after the addition was completed, the reaction mixture was stirred at room temperature overnight. An aqueous solution of 1 N hydrochloric acid was added to the reaction mixture, the mixture was extracted with chloroform, and then the organic layer was washed with water, an aqueous solution of saturated sodium bicarbonate and saturated brine solution, dried, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate=2:1) to obtain 7.20 g of an amide as a light yellow solid (yield: 60%).

[0364] 982 mg (7.11 mmol) of potassium carbonate and 982 mg (7.11 mmol) of 2-methoxy-5-methylphenol were added to a N,N -dimethylformamide solution (10 ml) of 200 mg (0.71 mmol) of the obtained amide, and the reaction mixture was stirred at 100°C for 12 hours. The reaction mixture was concentrated under reduced pressure, and the obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate=2:1) to obtain 278 mg of a nitro compound as a yellow solid (yield: 98%).

[0365] 2.0 g of iron powder was added to a mixture of an isopropanol solution (5 ml) of 247 mg (0.62 mmol) of the obtained nitro compound and an aqueous solution of saturated ammonium chloride (0.5 ml), and heated under reflux for 30 minutes. After cerite filtration, the reaction mixture was concentrated under reduced pressure, ethyl acetate and water were added to the residue, the organic layer was washed with water and saturated brine solution, dried, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate=2:1) to obtain 191 mg of the title compound as light yellow solids (yield: 84%).

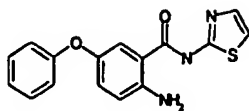
$^1\text{H NMR}(\text{CDCl}_3)$ δ : 2.24 (3H, s), 2.32 (3H, s), 3.84 (3H, s), 5.46 (1H, br), 6.52 (1H, d, $J=1.0\text{Hz}$), 6.66 (1H, s), 6.74 (1H, d, $J=8.9\text{Hz}$), 6.88 (2H, s), 7.06 (1H, dd, $J=2.6\text{Hz}$, 8.9Hz), 7.11 (1H, d, $J=2.6\text{Hz}$)

ESI-MS(m/e): 370 [$\text{M}+\text{H}$] $^+$

[0366] The compounds of Manufacturing Examples 84 to 117 were obtained as in Manufacturing Example 83.

Manufacturing Example 86

[0367]



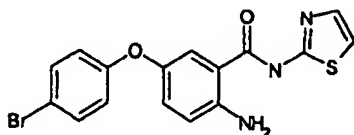
Preparation of 2-amino-5-phenoxy-N-thiazol-2-ylbenzamide

[0368] $^1\text{H NMR}(\text{CDCl}_3)$ δ : 5.53 (2H, br), 6.76 (1H, d, $J=8.9\text{Hz}$), 6.83-6.87 (3H, m), 7.01 (1H, t, $J=7.3\text{Hz}$), 7.08 (1H, dd, $J=2.3\text{Hz}$, 8.9Hz), 7.25-7.29 (3H, m), 7.32 (1H, d, $J=2.3\text{Hz}$), 11.61 (1H, br)

FAB-MS(m/e): 312 $[\text{M}+\text{H}]^+$

Manufacturing Example 87

[0369]



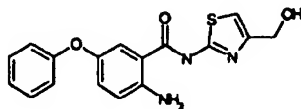
Preparation of 2-amino-5-(4-bromophenoxy)-N-thiazol-2-ylbenzamide

[0370] $^1\text{H NMR}(\text{CDCl}_3)$ δ : 5.60 (2H, br), 6.75-6.82 (3H, m), 6.96 (1H, d, $J=2.6\text{Hz}$), 7.06 (1H, dd, $J=2.6\text{Hz}$, 8.3Hz), 7.37-7.84 (4H, m)

FAB-MS(m/e): 392 $[\text{M}+\text{H}]^+$

Manufacturing Example 88

[0371]



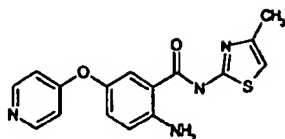
Preparation of 2-amino-5-phenoxy-N-(4-hydroxymethylthiazol-2-yl)benzamide

[0372] $^1\text{H NMR}(\text{CDCl}_3)$ δ : 4.38 (2H, d, $J=5.2\text{Hz}$), 5.14 (1H, t, $J=5.2\text{Hz}$), 5.53 (2H, br), 6.76 (1H, d, $J=8.9\text{Hz}$), 6.83-6.87 (2H, m), 7.01 (1H, t, $J=7.3\text{Hz}$), 7.08 (1H, dd, $J=2.3\text{Hz}$, 8.9Hz), 7.25-7.29 (3H, m), 7.32 (1H, d, $J=2.3\text{Hz}$), 11.61 (1H, br)

FAB-MS(m/e): 342 $[\text{M}+\text{H}]^+$

Manufacturing Example 89

[0373]



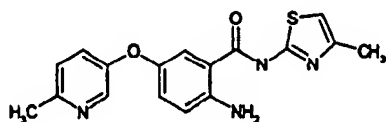
Preparation of 2-amino-5-(pyridin-4-yloxy)-N-(4-methylthiazol-2-yl)benzamide

[0374] $^1\text{H NMR}(\text{CD}_3\text{OD})$ δ : 2.32 (3H, d, $J=1.0\text{Hz}$), 6.44 (1H, s), 6.55 (2H, d, $J=7.6\text{Hz}$), 6.92 (1H, d, $J=8.9\text{Hz}$), 7.38 (1H, dd, $J=2.7\text{Hz}$, 8.9Hz), 7.87 (1H, d, $J=2.7\text{Hz}$), 8.03 (1H, d, $J=7.6\text{Hz}$)

FAB-MS(m/e): 327[M+H] $^+$

Manufacturing Example 90

[0375]



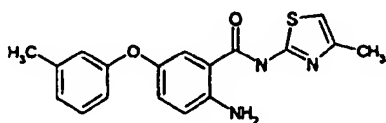
Preparation of 2-amino-5-(2-methylpyridin-5-yloxy)-N-(4-methylthiazol-2-yl)benzamide

[0376] $^1\text{H NMR}(\text{CD}_3\text{OD})$ δ : 2.29 (3H, d, $J=1.0\text{Hz}$), 2.47 (3H, s), 6.62 (1H, d, $J=1.0\text{Hz}$), 6.85 (1H, d, $J=8.9\text{Hz}$), 7.04 (1H, dd, $J=2.7\text{Hz}$, 8.9Hz), 7.21-7.28 (2H, m), 7.48 (1H, d, $J=2.7\text{Hz}$), 8.10 (1H, d, $J=2.6\text{Hz}$)

FAB-MS(m/e): 341[M+H] $^+$

Manufacturing Example 91

[0377]



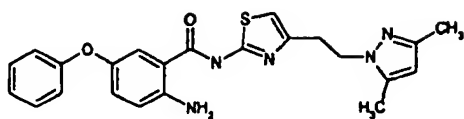
Preparation of 2-amino-5-(3-methylphenoxy)-N-(4-methylthiazol-2-yl)benzamide

[0378] $^1\text{H NMR}(\text{CDCl}_3)$ δ : 2.32 (6H, s), 6.53 (3H, d, $J=1.0\text{Hz}$), 6.71-6.77 (3H, m), 6.86-6.89 (1H, m), 7.08 (1H, dd, $J=2.7\text{Hz}$, 8.9Hz), 7.16-7.21 (2H, m)

FAB-MS(m/e): 340[M+H] $^+$

Manufacturing Example 92

[0379]



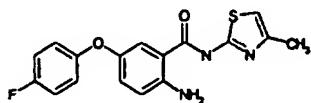
Preparation of 2-amino-5-phenoxy-N-[4-[2-(3,5-dimethylpyrazol-1-yl)ethyl]thiazol-2-yl]benzamide

[0380] $^1\text{H NMR}(\text{CDCl}_3)$ δ : 1.99 (3H, s), 2.22 (3H, s), 3.09 (2H, m), 4.21 (2H, m), 5.70 (1H, s), 6.43 (1H, s), 6.76 (1H, d, $J=9.0\text{Hz}$), 6.92 (1H, br.d, $J=7.5\text{Hz}$), 7.08 (2H, m), 7.22 (1H, br.s), 7.25-7.38 (2H, m)

FAB-MS(m/e): 434[$\text{M}+\text{H}$] $^+$

Manufacturing Example 93

[0381]



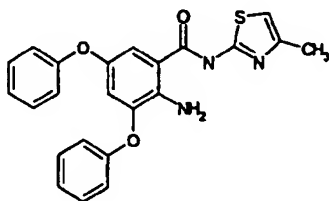
Preparation of 2-amino-5-(4-fluorophenoxy)-N-(4-methylthiazol-2-yl)benzamide

[0382] $^1\text{H NMR}(\text{CDCl}_3)$ δ : 2.14 (3H, s), 5.53 (2H, s), 6.51 (1H, s), 6.75 (1H, d, $J=9.2\text{Hz}$), 6.78-6.83 (2H, m), 6.93-6.97 (2H, m), 7.03-7.06 (2H, m)

FAB-MS(m/e): 344[$\text{M}+\text{H}$] $^+$

Manufacturing Example 94

[0383]



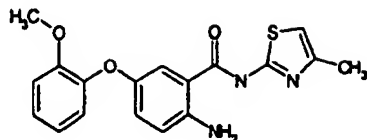
Preparation of 2-amino-3,5-diphenoxy-N-(4-methylthiazol-2-yl)benzamide

[0384] $^1\text{H NMR}(\text{CDCl}_3)$ δ : 2.31 (3H, d, $J=0.9\text{Hz}$), 6.53 (1H, d, $J=0.9\text{Hz}$), 6.76 (1H, d, $J=2.4\text{Hz}$), 6.88 (2H, dd, $J=1.0\text{Hz}$, 7.7Hz), 6.91-7.38 (9H, m)

FAB-MS(m/e): 418[$\text{M}+\text{H}$] $^+$

Manufacturing Example 95

[0385]



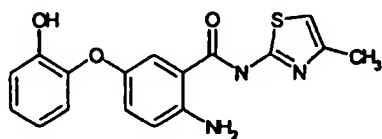
Preparation of 2-amino-5-(2-methoxyphenoxy)-N-(4-methylthiazol-2-yl)benzamide

[0386] $^1\text{H NMR}$ (CDCl_3) δ : 2.25-2.27 (3H, m), 3.86 (3H, s), 6.51 (1H, s), 6.73 (1H, d, $J=9.2\text{Hz}$), 6.80-6.90 (2H, m), 7.04-7.10 (4H, m)

FAB-MS(m/e): 356 $[\text{M}+\text{H}]^+$

Manufacturing Example 96

[0387]



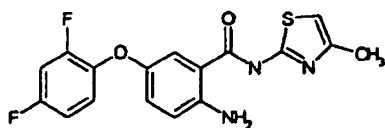
Preparation of 2-amino-5-(2-hydroxyphenoxy)-N-(4-methylthiazol-2-yl)benzamide

[0388] $^1\text{H NMR}$ (CDCl_3) δ : 2.27 (3H, s), 5.53 (1H, br), 6.52 (1H, s), 6.18-6.21 (3H, m), 6.94-7.06 (3H, m), 7.14 (1H, s)

FAB-MS(m/e): 342 $[\text{M}+\text{H}]^+$

Manufacturing Example 97

[0389]



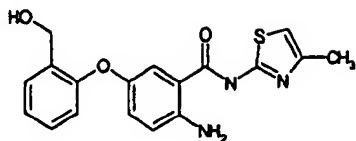
Preparation of 2-amino-5-(2,4-difluorophenoxy)-N-(4-methylthiazol-2-yl)benzamide

[0390] $^1\text{H NMR}$ (CDCl_3) δ : 2.15 (3H, s), 5.51 (1H, br), 6.51 (1H, d, $J=1.0\text{Hz}$), 6.71-6.93 (4H, m), 7.00-7.09 (2H, m)

FAB-MS(m/e): 362 $[\text{M}+\text{H}]^+$

Manufacturing Example 98

[0391]

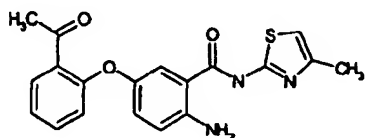


Preparation of 2-amino-5-(2-hydroxymethylphenoxy)-N-(4-methylthiazol-2-yl)benzamide

[0392] $^1\text{H NMR}(\text{CDCl}_3)$ δ : 2.20 (3H, d, $J=1.0\text{Hz}$), 4.73 (2H, s), 6.49 (1H, d, $J=1.0\text{Hz}$), 6.67 (1H, dd, $J=1.1\text{Hz}$, 8.1Hz), 6.72 (1H, d, $J=8.9\text{Hz}$), 7.01-7.16 (3H, m), 7.10 (1H, d, $J=2.6\text{Hz}$), 7.39 (1H, dd, $J=1.6\text{Hz}$, 7.5Hz)
 FAB-MS(m/e): 356 $[\text{M}+\text{H}]^+$

Manufacturing Example 99

[0393]

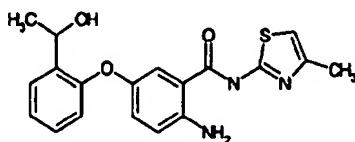


Preparation of 2-amino-5-(2-acetylphenoxy)-N-(4-methylthiazol-2-yl)benzamide

[0394] $^1\text{H NMR}(\text{CDCl}_3)$ δ : 2.16 (3H, s), 2.61 (3H, s), 5.63 (2H, brs), 6.50 (1H, s), 6.72 (1H, d, $J=8.4\text{Hz}$), 6.78 (1H, d, $J=8.4\text{Hz}$), 7.04-7.11 (2H, m), 7.20 (1H, s), 7.27-7.37 (1H, m), 7.79 (1H, dd, $J=7.7\text{Hz}$, 1.8Hz)
 FAB-MS(m/e): 368 $[\text{M}+\text{H}]^+$

Manufacturing Example 100

[0395]

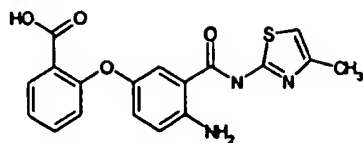


Preparation of 2-amino-5-[2-(1-hydroxyethyl)phenoxy]-N-(4-methylthiazol-2-yl)benzamide

[0396] $^1\text{H NMR}(\text{CDCl}_3)$ δ : 1.56 (3H, d, $J=6.6\text{Hz}$), 2.27 (3H, s), 4.59 (2H, brs), 5.21 (1H, q, $J=6.6\text{Hz}$), 6.52 (1H, s), 6.71 (1H, d, $J=8.6\text{Hz}$), 6.75 (1H, d, $J=8.6\text{Hz}$), 7.04-7.11 (2H, m), 7.14-7.18 (1H, m), 7.21 (1H, d, $J=2.9\text{Hz}$), 7.50 (1H, d, $J=7.3\text{Hz}$)
 FAB-MS(m/e): 370 $[\text{M}+\text{H}]^+$

Manufacturing Example 101

[0397]



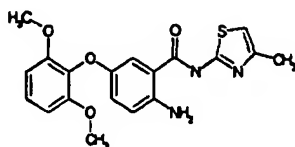
Preparation of 2-amino-5-(2-carboxyphenoxy)-N-(4-methylthiazol-2-yl)benzamide

[0398] $^1\text{H NMR}$ (DMSO- d_6) δ : 2.25 (3H, s), 6.73 (1H, s), 6.81 (1H, d, $J=8.9\text{Hz}$), 6.82 (1H, d, $J=7.6\text{Hz}$), 7.00 (1H, dd, $J=2.6\text{Hz}$, 8.9Hz), 7.07-7.12 (1H, m), 7.39-7.42 (1H, m), 7.62 (1H, d, $J=2.6\text{Hz}$), 7.71 (1H, d, $J=7.6\text{Hz}$)

FAB-MS(m/e): 370[$M+H$] $^+$

Manufacturing Example 102

[0399]



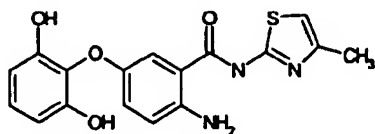
Preparation of 2-amino-5-(2,6-dimethoxyphenoxy)-N-(4-methylthiazol-2-yl)benzamide

[0400] $^1\text{H NMR}$ (CDCl_3) δ : 2.33 (3H, d, $J=1.1\text{Hz}$), 3.80 (6H, s), 6.52 (1H, d, $J=1.0\text{Hz}$), 6.65-6.71 (3H, m), 6.98-7.02 (2H, m), 7.11-7.18 (1H, m)

FAB-MS(m/e): 386[$M+H$] $^+$

Manufacturing Example 103

[0401]



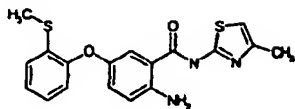
Preparation of 2-amino-5-(2,6-dihydroxyphenoxy)-N-(4-methylthiazol-2-yl)benzamide

[0402] $^1\text{H NMR}$ (CDCl_3) δ : 2.30 (3H, s), 6.47-6.50 (1H, m), 6.49 (1H, s), 6.54-6.58 (3H, m), 6.94-7.03 (2H, m)

FAB-MS(m/e): 358[$M+H$] $^+$

Manufacturing Example 104

[0403]



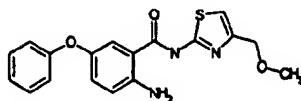
Preparation of 2-amino-5-(2-methylsulfonylphenoxy)-N-(4-methylthiazol-2-yl)benzamide

[0404] $^1\text{H NMR}$ (CDCl_3) δ : 2.26 (3H, d, $J=1.0\text{Hz}$), 2.46 (3H, s), 6.51 (1H, d, $J=1.0\text{Hz}$), 6.74 (1H, d, $J=9.4\text{Hz}$), 6.75 (1H, d, $J=9.2\text{Hz}$), 7.05-7.11 (4H, m), 7.23-7.26 (1H, m)

FAB-MS(m/e): 372 $[\text{M}+\text{H}]^+$

Manufacturing Example 105

[0405]



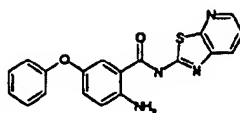
Preparation of 2-amino-5-phenoxy-N-(4-methoxymethylthiazol-2-yl)benzamide

[0406] $^1\text{H NMR}$ (CDCl_3) δ : 3.34 (3H, s), 4.24 (2H, s), 5.50-5.70 (2H, brs), 6.75 (1H, d, $J=8.4\text{Hz}$), 6.84 (2H, d, $J=7.6\text{Hz}$), 7.01 (1H, t, $J=7.6\text{Hz}$), 7.06-7.09 (2H, m), 7.25 (2H, t, $J=7.6\text{Hz}$), 10.4-10.5 (1H, brs)

FAB-MS(m/e): 356 $[\text{M}+\text{H}]^+$

Manufacturing Example 106

[0407]



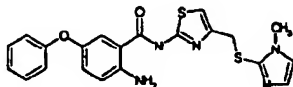
Preparation of 2-amino-5-phenoxy-N-thiazolo[5,4-b]pyridin-2-ylbenzamide

[0408] $^1\text{H NMR}$ (CDCl_3) δ : 6.79 (1H, d, $J=8.8\text{Hz}$), 6.83 (2H, d, $J=8.8\text{Hz}$), 7.04 (1H, t, $J=8.8\text{Hz}$), 7.10 (1H, dd, $J=2.4\text{Hz}$, 8.8Hz), 7.26-7.30 (3H, m), 7.31 (1H, dt, $J=4.8\text{Hz}$, 8.0Hz), 7.76 (1H, d, $J=8.0\text{Hz}$), 8.49 (1H, d, $J=4.8\text{Hz}$)

FAB-MS(m/e): 363 $[\text{M}+\text{H}]^+$

Manufacturing Example 107

[0409]



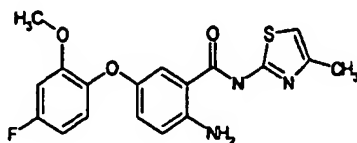
Preparation of 2-amino-5-phenoxy-N-[4-(1-methyl-1H-imidazol-2-yl)sulfanylmethyl]thiazol-2-yl]benzamide

[0410] $^1\text{H NMR}(\text{CDCl}_3)$ δ : 3.40 (3H, s), 4.15 (2H, s), 6.55 (1H, s), 6.75 (1H, d, $J=8.8\text{Hz}$), 6.87 (1H, s), 6.91 (2H, d, $J=7.2\text{Hz}$), 7.03-7.11 (3H, m), 7.25 (1H, dd, $J=2.8\text{Hz}$, 8.8Hz), 7.30 (2H, t, $J=7.2\text{Hz}$)

FAB-MS(m/e): 438 $[\text{M}+\text{H}]^+$

Manufacturing Example 108

[0411]



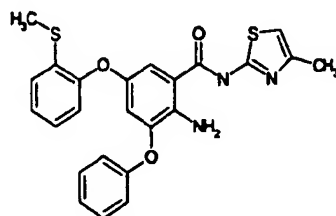
Preparation of 2-amino-5-(4-fluoro-2-methoxyphenoxy)-N-(4-methylthiazol-2-yl)benzamide

[0412] $^1\text{H NMR}(\text{CDCl}_3)$ δ : 2.31 (3H, d, $J=1.0\text{Hz}$), 3.84 (3H, s), 6.53 (1H, d, $J=1.0\text{Hz}$), 6.56-6.63 (1H, m), 6.73 (1H, d, $J=8.8\text{Hz}$), 6.74 (1H, d, $J=10.0\text{Hz}$), 6.84 (1H, dd, $J=5.7\text{Hz}$, 8.8Hz), 7.03 (1H, dd, $J=2.6\text{Hz}$, 8.8Hz), 7.06 (1H, d, $J=2.6\text{Hz}$)

FAB-MS(m/e): 374 $[\text{M}+\text{H}]^+$

Manufacturing Example 109

[0413]



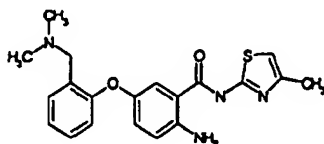
Preparation of 2-amino-3-phenoxy-5-(2-methylsulfanylmethoxy)-N-(4-methylthiazol-2-yl)benzamide

[0414] $^1\text{H NMR}(\text{CDCl}_3)$ δ : 2.27 (3H, s), 2.43 (3H, s), 6.53 (1H, s), 6.72-6.75 (1H, m), 6.77 (1H, d, $J=2.5\text{Hz}$), 6.90 (1H, d, $J=2.5\text{Hz}$), 7.03-7.07 (4H, m), 7.11-7.23 (2H, m), 7.33-7.38 (2H, m)

FAB-MS(m/e): 464 $[\text{M}+\text{H}]^+$

Manufacturing Example 110

[0415]



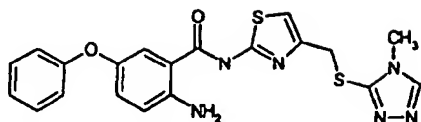
Preparation of 2-amino-5-(2-N,N-dimethylaminomethylphenoxy)-N-(4-methylthiazol-2-yl)benzamide

[0416] $^1\text{H NMR}(\text{CD}_3\text{OD})$ δ : 2.30 (3H, s), 2.56 (6H, s), 3.97 (2H, s), 6.63 (1H, s), 6.79-6.88 (2H, m), 7.02-7.11 (2H, m), 7.26-7.32 (1H, m), 7.43 (1H, d, $J=7.5\text{Hz}$), 7.48 (1H, s)

FAB-MS(m/e): 383 $[\text{M}+\text{H}]^+$

Manufacturing Example 111

[0417]

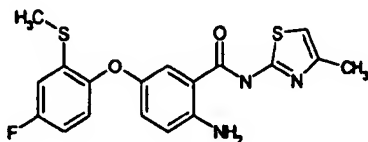


Preparation of 2-amino-5-phenoxy-N-[4-(4-methyl-4H-[1,2,4]triazol-2-ylsulfanylmethyl)thiazol-2-yl]benzamide

[0418] $^1\text{H NMR}(\text{CDCl}_3)$ δ : 3.45 (3H, s), 4.39 (2H, s), 5.50-5.70 (2H, brs), 6.76 (1H, d, $J=8.8\text{Hz}$), 6.82 (1H, s), 6.92 (2H, d, $J=7.6\text{Hz}$), 7.06-7.11 (2H, m), 7.20 (1H, d, $J=2.4\text{Hz}$), 7.31 (2H, t, $J=7.6\text{Hz}$), 8.09 (1H, s), 9.70-9.90 (1H, brs)
FAB-MS(m/e): 439 $[\text{M}+\text{H}]^+$

Manufacturing Example 112

[0419]

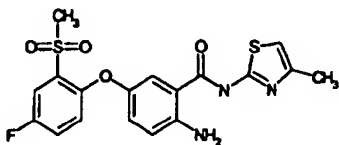


Preparation of 2-amino-5-(4-fluoro-2-methylsulfanylphenoxy)-N-(4-methylthiazol-2-yl)benzamide

[0420] $^1\text{H NMR}(\text{CDCl}_3)$ δ : 2.18-2.23 (3H, m), 2.42 (3H, s), 6.51 (1H, d, $J=0.9\text{Hz}$), 6.68-6.77 (3H, m), 6.84-6.93 (1H, m), 7.04 (1H, dd, $J=2.2\text{Hz}$, 8.6Hz), 7.10 (1H, d, $J=2.2\text{Hz}$)
FAB-MS(m/e): 390 $[\text{M}+\text{H}]^+$

Manufacturing Example 113

[0421]



Preparation of 2-amino-5-(4-fluoro-2-methylsulfonylphenoxy)-N-(4-methylthiazol-2-yl)benzamide

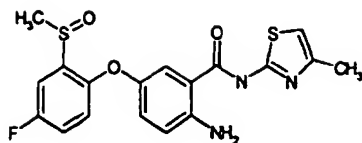
[0422] $^1\text{H NMR}(\text{CDCl}_3)$ δ : 2.18 (3H, s), 3.27 (3H, s), 5.69 (1H, br), 6.50 (1H, s), 6.75 (1H, d, $J=8.9\text{Hz}$), 6.81 (1H, dd, $J=4.0\text{Hz}$, 8.9Hz), 7.06 (1H, dd, $J=2.4\text{Hz}$, 8.9Hz), 7.13-7.22 (1H, m), 7.31 (1H, d, $J=2.4\text{Hz}$), 7.73 (1H, dd, $J=3.0\text{Hz}$, 7.3Hz)
FAB-MS(m/e): 422 $[\text{M}+\text{H}]^+$

Manufacturing Example 114

[0423]

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Preparation of 2-amino-5-(4-fluoro-2-methylsulfinylphenoxy)-N-(4-methylthiazol-2-yl)benzamide

15

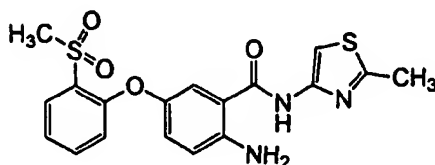
[0424] $^1\text{H NMR}$ (CDCl_3) δ : 2.28-2.34 (3H, m), 2.67 (3H, s), 6.54 (1H, s), 6.68-6.80 (2H, m), 7.01-7.09 (2H, m), 7.28 (1H, d, $J=2.7\text{Hz}$), 7.63-7.70 (1H, m)
FAB-MS(m/e): 406 $[\text{M}+\text{H}]^+$

Manufacturing Example 115

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[0425]

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Preparation of 2-amino-5-(2-methylsulfonylphenoxy)-N-(2-methylthiazol-4-yl)benzamide

35

[0426] $^1\text{H NMR}$ (CDCl_3) δ : 2.62 (3H, s), 3.33 (3H, s), 5.60 (2H, brs), 6.77 (1H, d, $J=8.8\text{Hz}$), 6.85 (1H, d, $J=8.1\text{Hz}$), 7.09 (1H, dd, $J=8.8\text{Hz}$, 2.6Hz), 7.20 (1H, dd, $J=7.7\text{Hz}$, 7.7Hz), 7.31 (1H, d, $J=2.6\text{Hz}$), 7.50 (1H, ddd, $J=8.1\text{Hz}$, 7.7Hz , 1.6Hz), 7.53 (1H, s), 8.05 (1H, dd, $J=7.7\text{Hz}$, 1.6Hz), 8.86 (1H, brs)
FAB-MS(m/e): 404 $[\text{M}+\text{H}]^+$

Manufacturing Example 116

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[0427]

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50

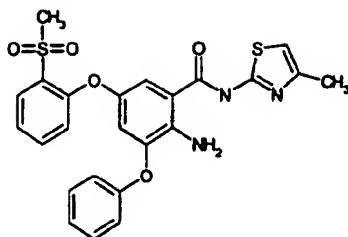
Preparation of 2-amino-5-(2-methylsulfinylphenoxy)-N-(2-methylthiazol-4-yl)benzamide

55

[0428] $^1\text{H NMR}$ (CDCl_3) δ : 2.64 (3H, s), 2.90 (3H, s), 5.57 (2H, brs), 6.71 (1H, d, $J=8.1\text{Hz}$), 6.76 (1H, d, $J=8.8\text{Hz}$), 7.02 (1H, dd, $J=8.8\text{Hz}$, 2.6Hz), 7.24 (1H, d, $J=2.6\text{Hz}$), 7.29 (1H, dd, $J=7.7\text{Hz}$, 7.7Hz), 7.37 (1H, ddd, $J=8.1\text{Hz}$, 7.7Hz , 1.7Hz), 7.54 (1H, s), 7.92 (1H, dd, $J=7.7\text{Hz}$, 1.7Hz), 8.73 (1H, brs)
FAB-MS(m/e): 388 $[\text{M}+\text{H}]^+$

Manufacturing Example 117

[0429]



Preparation of 2-amino-3-phenoxy-5-(2-methylsulfonylphenoxy)-N-(4-methylthiazol-2-yl)benzamide

[0430] $^1\text{H NMR}(\text{CDCl}_3)$ δ : 2.33 (3H, s), 3.28 (3H, s), 6.54 (1H, s), 6.81 (1H, d, $J=2.4\text{Hz}$), 6.86 (1H, d, $J=7.8\text{Hz}$), 7.05 (2H, d, $J=8.2\text{Hz}$), 7.16-7.22 (2H, m), 7.19 (1H, d, $J=2.4\text{Hz}$), 7.37 (2H, t, $J=8.2\text{Hz}$), 7.50 (1H, dt, $J=1.4\text{Hz}$, 7.8Hz), 8.04 (1H, dd, $J=1.4\text{Hz}$, 7.9Hz)

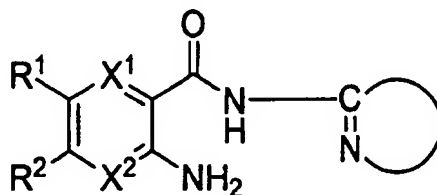
FAB-MS(m/e): 496 $[\text{M}+\text{H}]^+$

Industrial Applicability

[0431] The novel aminobenzamide derivative represented by the formula (I) or its pharmaceutically acceptable salt according to this invention has a glucokinase activation effect, and for example, is useful in the treatment and prevention of diabetes mellitus, and in the prevention of its complications such as diabetic nephropathy, diabetic retinopathy, diabetic neuropathy and diabetic arteriosclerosis.

Claims

1. A compound represented by the formula (I):



(I)

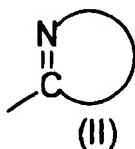
or a pharmaceutically acceptable salt thereof,
wherein

R^1 is $-\text{S}(\text{O})\text{p}-\text{A}$, $-\text{S}(\text{O})\text{q}-\text{B}$ or $-\text{O}-\text{D}$, wherein p and q, which are the same or different, each represent an integer from 0 to 2, A is a straight chain C1-C10 alkyl group which may be substituted by R^{10} , and B and D each independently represent R^{12} which may be substituted by R^{10} ;

R^2 is a hydrogen atom, a halogen atom, or a straight chain or branched C1-C6 alkyl group which may be substituted by R^{10} ;

X^1 and X^2 each independently represent N or CH, but cannot both be N;

the formula (II):



shows a monocyclic or bicyclic heteroaryl group which has a nitrogen atom adjacent to the carbon atom bonded to the amide group, and the heteroaryl group may be substituted by R¹⁰;

R¹⁰ is R¹¹, or a hydrocarbon group which may be substituted by R¹¹;

R¹¹ is a hydrogen atom, amino, carbamoyl, carbamoylamino, carbamoyloxy, carboxyl, cyano, sulfamoyl, trifluoromethyl, a halogen atom, hydroxyl, formyl, straight chain C1-C6 alkyl, C3-C6 cyclic hydrocarbon, aralkyl, N-aralkylamino, N,N-diaralkylamino, aralkyloxy, aralkylcarbonyl, N-aralkylcarbamoyl, aryl, arylthio, N-arylamino, aryloxy, arylsulfonyl, arylsulfonyloxy, N-arylsulfonylamino, arylsulfamoyl, N-arylcarbamoyl, aroyl, aroxy, C2-C6 alkanoyl, N-C2-C6 alkanoylamino, C1-C6 alkylthio, N-C1-C6 alkylsulfamoyl, N,N-di-C1-C6 alkylsulfamoyl, C1-C6 alkylsulfinyl, C1-C6 alkylsulfonyl, N-C1-C6 alkylsulfonylamino, C1-C6 alkoxy, C1-C6 alkoxycarbonyl or C1-C6 alkylamino; and

R¹² is phenyl, naphthyl, isoxazolyl, isothiazolyl, imidazolyl, oxazolyl, thiazolyl, thiadiazolyl, thienyl, triazolyl, tetrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrazolyl, pyrrolyl, pyranyl, furyl, furazanyl, imidazolidinyl, tetrahydrofuranyl, piperazinyl, piperidinyl, pyrrolidinyl, morpholino, isoquinolyl, isoindolyl, indolyl, ethylene dioxyphenyl, methylene dioxyphenyl, quinolyl, pyridothiazolyl, dihydroindolyl, tetrahydroquinolyl, tetrahydroisoquinolyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, benzotriazolyl or benzofuranyl.

2. The compound according to claim 1,

wherein, in formula (I),

R¹⁰ in A is R¹¹¹, or a hydrocarbon group which may be substituted by R¹¹¹;

R¹² in B is a phenyl, isothiazolyl, imidazolyl, oxazolyl, thiazolyl, thiadiazolyl, thienyl, triazolyl, tetrazolyl, pyridyl, pyrimidinyl, furyl, ethylene dioxyphenyl, methylene dioxyphenyl, pyridothiazolyl, benzimidazolyl, benzothiazolyl or benzotriazolyl, and the foregoing functional groups may each be substituted by R¹⁰;

R¹⁰ in B is R¹¹¹, or a hydrocarbon group which may be substituted by R¹¹¹;

R¹² in D is a phenyl, naphthyl, pyridyl, pyrazinyl, pyrimidinyl, ethylene dioxyphenyl, methylene dioxyphenyl or quinolyl, and the foregoing functional groups may each be substituted by R¹⁰;

R¹⁰ in D is R¹¹¹, or a hydrocarbon group which may be substituted by R¹¹¹;

R¹⁰ in R² is R¹¹¹, or a hydrocarbon group which may be substituted by R¹¹¹;

R¹⁰ in the heteroaryl group represented by formula (II) is R¹¹², or a hydrocarbon group which may be substituted by R¹¹²;

the heteroaryl group of formula (II) is thiazolyl, imidazolyl, isothiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, triazolyl, oxazolyl, isoxazolyl, pyrazinyl, pyridyl, pyrimidinyl, pyridothiazolyl or benzothiazolyl;

R¹¹¹ is a hydrogen atom, carbamoyloxy, carboxyl, cyano, trifluoromethyl, a halogen atom, hydroxyl, straight chain C1-C6 alkyl, saturated C3-C9 cyclic hydrocarbon, aralkyl, aryl, arylthio, aroyl, aroxy, C1-C6 alkylthio, C1-C6 alkylsulfonyl, C1-C6 alkoxy or C1-C6 alkoxycarbonyl; and

R¹¹² is a hydrogen atom, carbamoyl, carboxyl, sulfamoyl, trifluoromethyl, a halogen atom, hydroxyl, aralkyl, aryl, arylthio, arylsulfonyl, aroyl, aroxy, straight chain C1-C6 alkyl, C1-C6 alkylthio, C1-C6 alkylsulfinyl, C1-C6 alkylsulfonyl, C1-C6 alkoxy, C1-C6 alkoxycarbonyl or C3-C6 cycloalkyloxy.

3. The compound according to claim 1,

wherein, in formula (I),

R¹⁰ in A is R¹¹³, or a hydrocarbon group which may be substituted by R¹¹³;

R¹² in B is a phenyl, imidazolyl, oxazolyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidinyl, ethylene dioxyphenyl, methylene dioxyphenyl or pyridothiazolyl, and the foregoing functional groups may each be substituted by R¹⁰;

R¹⁰ in B is R¹¹³, or a hydrocarbon group which may be substituted by R¹¹³;

R¹² in D is a phenyl, naphthyl, pyridyl, ethylene dioxyphenyl or methylene dioxyphenyl, and the foregoing functional groups may each be substituted by R¹⁰;

R¹⁰ in D is R¹¹³, or a hydrocarbon group which may be substituted by R¹¹³;

R¹⁰ in R² is R¹¹³, or a hydrocarbon group which may be substituted by R¹¹³;

R¹¹³ is a hydrogen atom, carboxyl, trifluoromethyl, a halogen atom, hydroxyl, straight chain C1-C6 alkyl, saturated C3-C9 cyclic hydrocarbon, C1-C6 alkoxy, C1-C6 alkoxycarbonyl, C1-C6 alkylthio or C1-C6 alkylsulfonyl;

R¹⁰ in the heteroaryl group of formula (II) is R¹¹², or a hydrocarbon group which may be substituted by R¹¹²;
and

the heteroaryl group of formula (II) is thiazolyl, imidazolyl, isothiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, triazolyl, oxazolyl, isoxazolyl, pyrazinyl, pyridyl, pyrimidinyl, pyridothiazolyl or benzothiazolyl.

4. The compound according to claim 1,
wherein, in formula (I),
R¹⁰ in A is R¹¹³, or a hydrocarbon group which may be substituted by R¹¹³;
R¹² in B is a phenyl, imidazolyl, oxazolyl, thiazolyl, thiadiazolyl, triazolyl, pyridyl, pyrimidinyl, ethylene diox-
yphenyl, methylene dioxypheyl or pyridothiazolyl, and the foregoing functional groups may each be substituted
by R¹⁰;
R¹⁰ in B is R¹¹³, or a hydrocarbon group which may be substituted by R¹¹³;
R¹² in D is a phenyl, naphthyl, pyridyl, ethylene dioxypheyl or methylene dioxypheyl, and the foregoing
functional groups may each be substituted by R¹⁰;
R¹⁰ in D is R¹¹³, or a hydrocarbon group which may be substituted by R¹¹³;
R¹⁰ in R² is R¹¹³, or a hydrocarbon group which may be substituted by R¹¹³;
R¹¹³ is a hydrogen atom, carboxyl, trifluoromethyl, a halogen atom, hydroxyl, straight chain C1-C6 alkyl,
saturated C3-C9 cyclic hydrocarbon, C1-C6 alkoxy, C1-C6 alkoxycarbonyl, C1-C6 alkylthio or C1-C6 alkylsulfonyl;
R¹⁰ in formula (II) is R¹¹⁴, or a hydrocarbon group which may be substituted by R¹¹⁴; and
R¹¹⁴ is a hydrogen atom, carboxyl, trifluoromethyl, a halogen atom, hydroxyl, aryl, arylthio, straight chain
C1-C6 alkyl, C1-C6 alkylthio, C1-C6 alkoxy or C1-C6 alkoxycarbonyl.
5. The compound according to claim 4, wherein R¹ in formula (I) is -S(O)_p-A or -S(O)_q-B.
6. The compound according to claim 4, wherein R¹ in formula (I) is -O-D.
7. The compound according to claim 3, wherein both X¹ and X² in formula (I) are CH.
8. The compound according to claim 3, wherein either X¹ or X² in formula (I) is a nitrogen atom.
9. The compound according to claim 4, wherein both X¹ and X² in formula (I) are CH.
10. The compound according to claim 4, wherein either X¹ or X² in formula (I) is a nitrogen atom.
11. A glucokinase activator containing as an active constituent the compound according to any one of claims 1 to 10.
12. A treatment agent and/or preventive agent for diabetes mellitus or obesity containing as an active constituent the
compound according to any one of claims 1 to 10.
13. A treatment agent and/or preventive agent for diabetes mellitus containing as an active constituent the compound
according to any one of claims 1 to 10.
14. A treatment agent and/or preventive agent for obesity containing as an active constituent the compound according
to any one of claims 1 to 10.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP03/03656

A. CLASSIFICATION OF SUBJECT MATTER

Int.Cl.⁷ C07D277/46, 277/56, 401/12, 417/12, 417/14, 513/04,
417/06, A61K31/426, 31/427, 31/433, 31/437, 31/4439,
31/506, A61P3/04, 3/10, 43/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int.Cl.⁷ C07D277/46, 277/56, 401/12, 417/12, 417/14, 513/04,
417/06, A61K31/426, 31/427, 31/433, 31/437, 31/4439,
31/506, A61P3/04, 3/10, 43/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAPLUS (STN), CAOLD (STN), REGISTRY (STN), MEDLINE (STN),
BIOSIS (STN), EMBASE (STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	WO 00/039118 A1 (ELI LILLY AND CO.), 06 July, 2000 (06.07.00), Page 354 & CA 2361149 A & EP 1140903 A1 & JP 2002-533454 A	1-10 11-14
Y	WO 01/44216 A1 (F.HOFFMANN-LA ROCHE A.G.), 21 June, 2001 (21.06.01), Pages 22 to 73 & AU 2365201 A1 & JP 2003-516980 A & US 6353111 B1	11-14
Y	WO 00/58293 A1 (F.HOFFMANN-LA ROCHE A.G.), 05 October, 2000 (05.10.00), Pages 42 to 252, 331 to 333 & AU 3963000 A1 & JP 2002-540195 A & US 2001/39344 A & EP 1169312 A1	11-14

☒ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"I" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search
30 May, 2003 (30.05.03)

Date of mailing of the international search report
17 June, 2003 (17.06.03)

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP03/03656

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 01/10865 A1 (Takeda Chemical Industries, Ltd.), 15 February, 2001 (15.02.01), Page 26; tables & EP 1205478 A1 & JP 2001-114690 A	12-14
Y	JP 58-69812 A (Chugai Pharmaceutical Co., Ltd.), 26 April, 1983 (26.04.83), Page 1; tables (Family: none)	12,13